Adverse effects of treatment in long-term survivors of breast cancer

Hooning, M.J.

2008

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Maartje J. Hooning

The work presented in this thesis was supported by the Dutch Cancer Society (grant NKI 98-1833). Financial support by the Dutch Cancer Society for this publication is gratefully acknowledged.

ISBN: 978-90-8559-340-9

Cover illustration: Agnes van der Gaag 2007

Layout and printing by Optima Grafische Communicatie, Rotterdam, The Netherlands

VRIJE UNIVERSITEIT

Adverse effects of treatment in long-term survivors of breast cancer

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor
aan de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. L.M. Bouter,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de faculteit der Geneeskunde
op woensdag 9 januari 2008 om 15.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Maartje Joanneke Hooning

geboren te Haarlem

promotor: prof.dr.ir. F.E. van Leeuwen

copromotor: dr. B.M.P. Aleman

Contents

1 Introduction

Background

Breast cancer is by far the most frequent cancer among women in Western Europe and Northern America.[1] In the Netherlands 11,687 new female breast cancers were diagnosed in 2003.[2] For the period 1999–2003, cumulative risk of breast cancer up to age 75 years was 9.8% for a Dutch woman.[2] Incidence rates have doubled since they became available in 1955 from the first Dutch cancer registry, in the south of the Netherlands[3,4] (Figure 1.1). Over the last decades the prevalence of almost all known risk factors for breast cancer has changed into an unfavorable direction: older age at first birth, reduced number of pregnancies, shorter duration of breast feeding, earlier menarche, less physical activity, more overweight, more use of postmenopausal estrogen therapy and increased alcohol consumption.[5] Simultaneously, breast cancer mortality remained almost unchanged, showing only a slight increase in the mid-1970s, and a decrease again since the 1980s[3,4,6] (Figure 1.1). The discrepancy between mortality and incidence trends is caused by improved survival, which on its turn is due to more effective treatment, earlier diagnosis and the introduction of a nationwide screening program in 1990. Figure 1.2 shows that relative survival has gradually increased over the years[5]; stage-specific survival has also increased.[7] Consequently, the prevalence of breast cancer has increased as well (Figure 1.3). In 2000 the age-adjusted prevalence of female

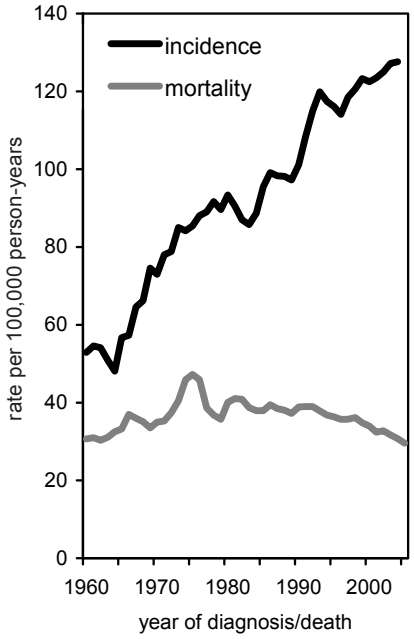

Figure 1.1. Trends in incidence and mortality of breast cancer per 100,000 women, with age-adjustment by direct standardization according to the European Standardized Rate (ESR), for the period 1960 – 2004, from the Eindhoven Cancer Registry[4]

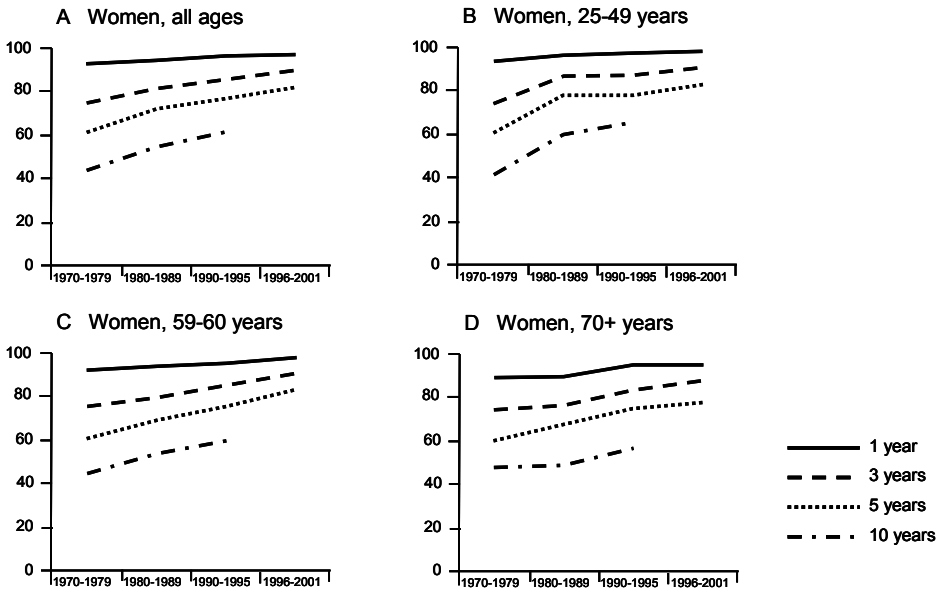

Figure 1.2. Trends in 1-, 3-, 5- and 10-year relative survival of breast cancer in women, for the period 1970 – 2001, for different age groups, from the Eindhoven Cancer Registry[5]

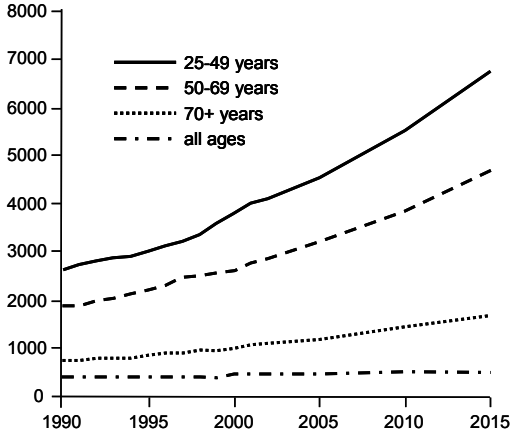

Figure 1.3. Trends and prognoses of breast cancer prevalence per 100,000 women in the Netherlands, for the period 1990 – 2015[5]

breast cancer was 1,000 per 100,000 women; in absolute numbers this implies that more than 92,000 women alive in 2000 had been diagnosed with breast cancer over the last 20 years[1]. In view of the improved survival of breast cancer it has become exceedingly important to evaluate possible late adverse effects of treatment. Knowledge of long-term treatment ef-

1. 20-year prevalence: defined by all women diagnosed with breast cancer between 01-01-1982 and 31-12-2001, and still alive by 01-01-2002; women diagnosed before 1982 were excluded.

fects may lead to modification of treatment regimens, techniques or indications in order to decrease the risk of adverse effects in future patients, while maintaining equal levels of therapeutic effectiveness.

Of all late complications of treatment, cardiovascular disease and second malignancies are generally considered to be the most serious since they do not only cause substantial morbidity but also considerable mortality. Increased risks of cardiac disease and second cancers have been observed after both radiotherapy and chemotherapy.[8,9] First reports on radiation-induced heart disease were published in the 1960s and described cardiac complications resulting from mediastinal irradiation in patients cured of Hodgkin's disease.[10] The clinical manifestation of radiation-related damage to the heart involves coronary artery disease, pericardial disease, myocardial dysfunction, valvular heart disease and electrical conduction abnormalities.[8,10] It was not until the end of the 1980s, that adverse effects of radiotherapy on the heart in survivors of breast cancer were recognized. Radiotherapy techniques for treating the breast/chest wall and draining lymph nodes could result in a relatively high dose being delivered to a substantial volume of heart. Evidence for increased cardiovascular mortality from breast cancer radiotherapy regimens was provided by several randomized-controlled trials and observational studies, with relative risk estimates ranging from 1.1 to 2.2.[11]

With respect to chemotherapy, regimens containing anthracyclines are notorious for their cardiotoxicity[8], with a clinical presentation of acute, subacute or late cardiomyopathy. The oldest adjuvant regimen used for breast cancer consisted of cyclophosphamide, methotrexate and fluorouracil. Administration of high doses of cyclophosphamide aimed for immunosuppression before bone marrow transplantation, has been associated with increased risk of cardiomyopathy, but there are no reports on risks following standard adjuvant doses. Methotrexate is not known for causing heart problems. Fluorouracil has been associated with cardiotoxicity, featuring cardiac failure, arrhythmia and ischemia-like symptoms. Usually these problems are reported during treatment and disappear within days to weeks after cessation of infusion.[8] In general, follow-up of the studies conducted so far was too short to investigate the long term effects of chemotherapy.

Most studies reporting on increased risk of cardiovascular disease after breast cancer treatment concern radiation techniques from the 1960s and early 1970s, which are now considered as suboptimal.[12-16] Improvements in radiotherapy treatment techniques have led to a general reduction in dose to the heart but it is unknown whether contemporary radiotherapy methods lead to less increased risk of cardiovascular disease. Recent studies on more modern regimens administered during the 1980s show inconsistent results (Table 1.1) and few long-term data are available.[17-27] Furthermore, till 2002 only cardiac mortality, not morbidity, has been investigated in most studies. Yet, cardiac morbidity has a serious impact on the life expectancy and quality of life of long-term survivors. Also, incidence studies have some methodologic advantages over studies evaluating mortality. Clearly, there are more events to analyze and usually the follow-up time needed to observe sufficient numbers of cardiovascu-

Table 1.1. Overview of studies on risk of cardiac disease after RT regimens applied during the 1970s and 1980s[17-27].

First author	Study size	Treatment period	RT regimen	Method of comparison	RR: incidence	RR: mortality	Refs
Rutqvist '90	54 617	'70 – '85	~ 50% RT	L vs R-sided tumors	_	MI: 1.09 (1.02 – 1.17)	17
Rutqvist '98	5 680	'76 – '87	Postlumpectomy	RT (12%) vs no RT	MI: 0.6 (0.4 – 1.2)	MI: 0.4 (0.2 – 1.1)	18
Højris '99	3 083	'82 – '90	Postmastectomy	RT vs no RT	IHD: 0.86 (0.6 – 1.3)	IHD: 0.84 (0.4 – 1.8)	19
Paszat '99	25 570	'82 – '87	Postlumpectomy	L vs R-sided RT	_	MI: 2.10 (1.11 – 3.95)	20
Vallis '02	2 128	'82 – '88	Postlumpectomy	L vs R-sided RT	MI: no difference	MI: no difference	21
Darby '03	89 407	'70 – '96	~ 30% RT	L vs R-sided tumors	_	CVD*: 1.10 (1.03 – 1.18)	22
Giordano '05	27 283	'73 – '89	Several	L vs R-sided RT	_	IHD†: 1.5 (1.19 – 1.87)	23
Darby '05	115 165	'73 – '01	Several	L vs R-sided RT	_	CVD*: 1.44 (1.26 – 1.65)	24
Patt '05	16 270	'86 – '93	Several	L vs R-sided RT	IHD: 1.05 (0.94 – 1.16)	_	25
EBCTCG '06	32 800	'61 – '91	Several	RT vs no RT	_	CVD: 1.27 (2p = 0.0001)	26
Harris '06	961	'77 – '94	Postlumpectomy	L vs R-sided RT	IHD: 2.7 (1.7 – 4.5)	CVD: no difference	27

Abbreviations: RT, radiotherapy; RR, rate ratio; MI, myocardial infarction; CVD, cardiovascular disease; IHD, ischemic heart disease; L, left; R, right.

*Cardiac mortality among 10-year survivors.

†IHD mortality among women treated for breast cancer in 1979; for women diagnosed after 1979 mortality from ischemic heart disease declined by 6% for each successive year until 1988 (HR, 0.79; 95% CI: 0.52 – 1.18).

lar events will be shorter. However, only few investigators have attempted to study incidence of cardiovascular disease in breast cancer patients because in most countries there are no registries available with information on the occurrence of cardiac diseases. Obviously, the collection of individual patient data on cardiovascular disease during follow-up would be an ambitious undertaking. The lack of reference rates would also hamper a comparison with the general population.

In breast cancer patients treated with adjuvant radiotherapy, not only the heart but also the common carotid arteries may be exposed, depending on the fields applied. Head and neck cancer patients and survivors of Hodgkin's lymphoma treated with local radiotherapy on the neck experience an increased risk of stroke during long-term follow-up.[28,29] By analogy, breast cancer patients are potentially at risk for radiation-related stroke. Until now, no study has reported on the incidence of ischemic stroke in relation to specific radiation regimens for breast cancer.

With regard to second cancers following breast cancer, treatment-related excess risks have been observed for cancers of the contralateral breast,[26,30,31] lung,[26,32-34] esophagus,[26,35] endometrium,[36-38] soft tissue sarcoma,[26,39] and leukemia.[26,40,41] Some recent studies on Hodgkin's disease patients have reported an increased risk of solid tumors after a combined regimen of chemotherapy and radiotherapy.[42-44] So far, it is unknown whether these findings apply to breast cancer, as well. Although some studies have shown an association between radiation and the risk of contralateral breast cancer, the possible influence of modern radiotherapy on the development of contralateral breast cancer after treatment for breast cancer remains

unclear. Two large case-control studies evaluated the effect of radiation treatment administered for the initial breast cancer in the periods 1935-1982 and 1943-1978, respectively, and found that radiotherapy did not contribute to the risk of contralateral disease among women treated after the age of 45.[30,45] In the study based on the Connecticut Tumor Registry, however, significantly elevated risks were observed for women who underwent irradiation before the age of 45, with a radiation-associated relative risk of 1.85 among those who survived for at least 10 years.[30] Significant excess risk in women irradiated at a young age was not found in the Danish study, possibly because it included fewer women under the age of 45.[45] A greater risk increase for radiation-associated breast cancer when exposed at younger age has also been observed in the atomic bomb survivors[46] and patients treated for Hodgkin's lymphoma.[47]

Modern radiotherapy techniques for breast cancer deliver a lower dose to the contralateral breast than the techniques applied in the two case-control studies. Only few studies have examined whether RT as applied from the 1980s onwards affects the risk of CBC.[26,31,48-51] So far, results are inconclusive. Some studies have provided evidence that adjuvant CT may reduce the risk of CBC.[9,48,52,53] This further complicates analysis of potential risk factors.

Aims of the thesis

General aim of the present study was to evaluate the long-term risks, both in terms of incidence and mortality, of second cancers, heart disease and cerebrovascular disease in survivors of breast cancer.

We aimed to examine whether risks of second cancers, cardiac and cerebrovascular disease were increased as compared with the incidence in the general population, stratified by:

- follow-up interval,
- treatment modality,
- age at first treatment and
- calendar period of first treatment.

More specifically, we wanted to answer the following questions:

- does modern radiotherapy increase the risks of contralateral breast cancer, cardiac and cerebrovascular disease (compared to surgery alone);
- to what extent is the type of radiation field administered related to
  - risk of contralateral breast cancer
  - risk of cardiac disease and
  - risk of cerebrovascular disease;
- are younger women (<45 years of age at exposure) at higher risk of radiation-associated contralateral breast cancer than those exposed at older ages?

Furthermore, does chemotherapy

- increase the risk of solid tumors,
- increase the risk of cardiac disease, and
- decrease the risk of contralateral breast cancer?

Finally, we assessed potential interaction of

- cardiovascular risk factors with radiotherapy on the risk of cardiac disease, and of
- family history of breast cancer with radiotherapy on the risk of contralateral breast cancer.

To achieve these aims, we conducted the Late Effects Breast Cancer (BC) Study, a retrospective cohort study consisting of 7425 1-year survivors of breast cancer treated from the 1970s through the 1980s in two major cancer centers in the Netherlands. This thesis presents the results of all studies undertaken in view of the Late Effects BC Study. Unique features include near-complete and long-term follow-up of more than 25 years, collection of detailed information on both primary and follow-up treatment, including specific irradiated regions and chemotherapeutic agents, and of data on known cardiovascular risk factors. We report on both mortality and morbidity from cardiac and cerebrovascular disease, contralateral breast cancer, and on late mortality from breast cancer and various second cancers.

Outline of the thesis

Chapter 2 describes cause-specific mortality among breast cancer patients in the Late Effects BC Study, and gives an overview of the main causes of death occurring in excess in breast cancer patients, with special attention for mortality from second malignancies, cardiovascular disease, stroke and breast cancer. Analyses comprised external comparison with general population rates, including evaluation of trends in risk by age at diagnosis of breast cancer and follow-up time. The Cox proportional hazards model was used for internal comparison between different treatments.

The long-term risk of contralateral breast cancer is addressed in chapter 3, focusing on the effect of different radiation regimens, chemotherapy and family history of breast cancer. Comparisons with general population rates were stratified by age and follow-up time, and the effects of different treatments were analyzed with the Cox proportional hazards model.

The incidence of cardiac disease is the outcome of interest evaluated in chapter 4. Since the increase in risk of (cardio-)vascular events associated with radiotherapy appears to emerge especially after 10 or more years we selected all 10-year survivors of breast cancer and assessed long-term cardiovascular disease risk according to specific radiation fields. Mean cardiac dose was estimated for the various irradiated regions in order to evaluate a dose-response relationship. Also the long-term effects of chemotherapy were examined. Furthermore, we incorporated known cardiovascular risk factors into analyses. External comparisons with general population rates included assessment of trends in risk by age and follow-up time.

Risk of stroke, as another manifestation of vascular disease, was evaluated in a separate study presented in chapter 5. Since we were most interested in a radiation-related effect, we again restricted the study population to patients who had survived breast cancer for at least 10 years. Also, we accounted for known cerebrovascular risk factors in the Cox proportional hazards model. Comparisons with general population rates were stratified by age and follow-up time.

With the increasing use of breast conserving therapy for both infiltrating carcinoma and ductal carcinoma in situ, and the growing number of patients presenting with stage 0/1 disease, requiring only radiation of the breast, the possible (late) cardiac complications of this type of therapy have become more important. To address this question we combined data on patients treated with breast tangentials from the Late Effects BC Study with data from patients treated with the same regimen from four other hospitals. In this study, reported in chapter 6, we assessed the effect of tangential breast irradiation on cardiovascular disease incidence by comparing left- and right-sided breast cancer patients. Subsequently, we measured in all left-sided breast cancer patients the maximum heart distance on simulator films as a proxy for irradiated heart volume[54] and evaluated whether increasing maximum heart distance was associated with greater risk of cardiovascular disease.

The general discussion in chapter 7 considers some important issues related to the Late Effects BC Study that have not been evaluated in the separate studies and concludes with implications for clinical practice of today and recommendations for future research.

A summary in English and Dutch concludes this thesis.

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2 Cause-specific mortality in long-term survivors of breast cancer: a 25-year follow-up study

Maartje J. Hooning, Berthe M.P. Aleman, Agnes J.M. van Rosmalen, Marianne A. Kuenen, Jan G.M. Klijn, Flora E. van Leeuwen

Int J Radiat Oncol Biol Phys 2006; 64: 1081-91

Abstract

Purpose

To assess long-term cause-specific mortality in breast cancer patients.

Patients and Methods

We studied mortality in 7425 patients treated for early breast cancer between 1970 and 1986. Follow-up was 94% complete until January 2000. Treatment-specific mortality was evaluated by calculating standardized mortality ratios (SMRs) based on comparison with general population rates and by using Cox proportional hazards regression.

Results

After a median follow-up of 13.8 years, 4160 deaths were observed, of which 76% were due to breast cancer. Second malignancies showed a slightly increased SMR of 1.2 (95% confidence interval [CI]: 1.0 - 1.3). Radiotherapy (RT) as compared with surgery was associated with a 1.7-fold (95% CI: 1.2 - 2.5) increased mortality from cardiovascular disease (CVD). After postlumpectomy RT, no increased mortality from CVD was observed (hazard ratio = 1.0; 95% CI: 0.5 - 1.9). Postmastectomy RT administered before 1979 and between 1979 and 1986 was associated with a 2-fold (95% CI: 1.2 - 3.4) and 1.5-fold (95% CI: 0.9 - 2.7) increase, respectively. Patients treated before age 45 experienced a higher SMR (2.0) for both solid tumors (95% CI: 1.6 - 2.7) and CVD (95% CI: 1.3 - 3.1).

Conclusion

Currently, a large population of breast cancer survivors is at increased risk of death from CVDs and second cancers, especially when treated with RT at a young age. Patients irradiated after 1979 experience low (postmastectomy RT) or no (postlumpectomy RT) excess mortality from CVD.

Introduction

Over the past decades, survival of breast cancer patients has substantially improved as a result of earlier diagnosis, introduction of combination chemotherapy (CT) and hormonal treatment (HT), and refinement of radiation techniques.[1-4] At the same time, however, several studies have demonstrated that radiotherapy (RT) and some types of CT can increase the risk of cardiovascular disease[5-7] (CVD) and of second primary cancers.[8-12] Most studies reporting on increased risk of CVD concern radiation techniques from the 1960s and early 1970s that are now considered as suboptimal. Recent studies on more modern regimens administered during the 1980s show inconsistent results.[13-18] With regard to breast-conserving therapy (BCT), the sparse literature suggests that the risk of CVD is negligible in the case of breast radiation only.[14,15,17] However, few long-term data are available. This highlights the need for studies of patients treated with modern radiation therapy methods.

With regard to second cancers, treatment-related excess risks have been observed for cancers of the contralateral breast (CLBC),[19] lung,[11,20-22] endometrium,[23-25] soft tissue sarcoma,[26] and leukemia.[27-28] Some recent studies on Hodgkin's disease patients have reported an increased risk of solid tumors after a combined regimen of CT and RT.[29-31] Long-term follow-up studies are needed to investigate whether these findings apply to breast cancer, as well.

Therefore, in the present study, we report on treatment-specific mortality during long-term follow-up of a large population of breast cancer patients ($n = 7425$) treated between the 1970s and 1980s in two major cancer centers in the Netherlands. We focus on causes of death from cardiovascular disease, second primary cancers, and on late mortality from breast cancer.

The added value of our study is defined by the very long follow-up, the detailed information on treatments received, and by the relatively large proportion of young patients (30% were younger than 45 years at the time of breast cancer diagnosis).

Patients and methods

Data collection procedures

The cohort consisted of two groups of patients, all 1-year survivors, admitted to the Netherlands Cancer Institute (NKI) or the Erasmus MC, Daniel den Hoed Cancer Center (DDHK) for treatment of Stage I , II, and IIIA female breast cancer: Group 1: all patients first treated in the period 1970-1975, age < 66 at diagnosis ($n = 2001$); Group 2: a stratified sample of all patients first treated between 1976 and 1986, age < 71 at diagnosis ($n = 5524$). This group (Group 2) consisted of all patients treated with surgery only, all patients who received adjuvant CT, and, for reasons of efficiency, a sample of all patients treated with surgery and RT, stratified by age - this was by far the largest group. To evaluate excess morbidity and mortality after treatment,

we needed to examine a group of patients with prolonged follow-up. Therefore, an age limit of 65 years at diagnosis was chosen for patients in Group 1.

All patients were identified through the hospital-based cancer registries of the two centers. Data were collected on the following variables: date of birth, date of breast cancer diagnosis, diagnosis and treatment of previous cancers, tumor histology, axillary lymph node involvement, treatment, complete remission, date of first recurrence, dates and diagnosis of second cancers, date of death or of last known medical status and (underlying) cause of death, according to the International Classification for Diseases, 9th revision.

Treatment information included the following: dates of primary and follow-up treatment, treatment modalities for primary breast cancer and for recurrent disease (type of surgery, RT yes/no, CT yes/no, HT yes/no), and names of cytostatic drugs. In the case of a second cancer, we obtained the pathology report to rule out the possibility of a metastatis of the primary breast cancer.

In total, our study population contained 7525 patients. We excluded patients who had been irradiated above the diaphragm or treated with CT for cancer or a benign condition before the diagnosis of breast cancer (n = 100), thus reducing the study population to 7425 patients. For this group, we updated follow-up information until at least January 1, 2000. To establish the medical status of patients lost to follow-up in the two cancer centers (n = 2965) a questionnaire was mailed to specialists in other hospitals and general practitioners. For patients lost to follow-up both at their last treating hospital and at their general practitioner's office, we contacted the municipal registries to obtain vital status, resulting in 99% completeness for all patients. The cause of death was known for 94% of all deceased patients.

Treatment

During the 1970s, standard treatment for Stage I, II, and IIIA breast cancer at NKI and DDHK was surgery (modified or radical mastectomy) with or without RT. As of 1975, adjuvant systemic treatment was introduced for node-positive patients: combination chemotherapy for premenopausal patients and, from 1976 onward, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of CMF (cyclophosphamide, methotrexate, and fluorouracil) during the whole study period. Until 1980, 12 cycles were administered; after 1980, only 6 were given. In 1979 breast-conserving therapy was introduced in both hospitals; BCT consisted of wide local excision and axillary lymph node dissection, followed by irradiation of the whole breast.

The radiotherapy regimen depended on the type of surgery and the stage of disease. There were some diffences between the two cancer centers. At the NKI, irradiation of the ipsilateral internal mammary chain lymph nodes (IMC) was given to patients with centrally or medially located tumors and/or axillary lymph node metastases during the whole study period. In case of extensive axillary nodal metastases, the axilla and supraclavicular nodes were irradiated, as well. Chest wall irradiation was given in case of an incomplete resection or an extensive

primary tumor. For patients receiving breast-conserving therapy, the breast was always irradiated postoperatively. In the DDHK, 60% of patients with centrally or medially located tumors and/or axillary lymph node metastases received ipsilateral IMC field treatment. Indications for irradiation of axilla, supraclavicular nodes, chest wall, or breast were comparable to the indications used in the NKI. The dose to the internal mammary chain varied from 40 Gy in 15 fractions in 3 weeks to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and electrons; the chest wall received doses between 35 Gy and 45 Gy in 15 to 20 fractions, using electrons. Breast irradiation consisted of a dose of 50 Gy in 25 fractions using two tangential photon beams (4-8 MV or ^{60}Co), followed by a boost of 15-25 Gy to the tumor bed, preferably using an iridium implant.

Statistical analysis

We compared cause-specific mortality in the study population with that in the general population. In this person-years type of analysis, the ratio of the observed (O) and expected (E) number of deaths in the study population was determined using age-specific, gender-specific, and calendar period-specific mortality rates from Statistics Netherlands. Time at risk began 1 year after the start of first treatment and ended at the date of death or date of last known vital status. The confidence limits of the O/E ratio or Standardized Mortality Ratio (SMR) were obtained with the use of the Poisson distribution of the observed numbers.[32] Absolute excess risk (AER) is the most appropriate risk measure to judge which specific causes contribute most to excess mortality. We calculated the AER by subtracting the expected number of deaths in our cohort from the number observed, and dividing by person-years at risk (expressed per 10,000 person-years).[33]

To assess treatment effects on cause-specific mortality, we established five mutually exclusive treatment categories, defined by all treatments received up to 1 year before end of follow-up: (*1*) surgery only, (*2*) RT with or without surgery, (*3*) RT and CT with or without surgery, (*4*) RT and HT with or without surgery, and (*5*) RT and CT and HT with or without surgery. Treatments given in the last year of follow-up were excluded, because we did not want to take into account salvage treatments received for recurrent disease during the last period in life. Furthermore, to evaluate the independent effects of primary treatment, we did an analysis restricted to the group of patients that never received treatment for recurrent disease.

Overall cumulative (actuarial) probabilities of death were estimated as a function of time since initial treatment using the Kaplan-Meier method.[34] The Cox proportional hazards model[35] was used to quantify the effects of different treatments on mortality, adjusting for several covariates (age at treatment, treatment period). Cox's models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL).

Results

Table 2.1 shows the general characteristics of the study population. Almost half of all patients were treated in the period 1981-1986. The use of BCT increased during the study period, from only 1% during the years 1970-1975, to 7% during 1976-1980, and up to 45% in the period

Table 2.1. Characteristics of the Dutch Late Effects BC Study

	Characteristic	No. of BC patients	%
No. of patients		7425	100
Hospital	NKI	3296	44.4
	DDHK	4129	55.6
Age at BC diagnosis (years)	< 45	2242	30.2
	45 - 54	2640	35.6
	≥ 55	2543	34.2
Year of first treatment of BC	1970 - 75	2012	27.1
	1976 - 80	1850	24.9
	1981 - 86	3563	48.0
Axillary node involvement (at diagnosis)	Node negative	3486	46.9
	Axillary node pos., subclav. neg.	3187	42.9
	Subclav. pos.	591	8.0
	Unknown	161	2.2
Laterality	Left	3822	51.5
	Right	3503	47.2
	Bilateral	100	1.3
Primary treatment category	Surgery only	872	11.7
	RT (+ surgery)	5105	68.8
	RT + CT (+ surgery)	1144	15.4
	RT + HT (+ surgery)	78	1.1
	RT + CT + HT (+ surgery)	163	2.2
	Other/unknown	63	.8
Treatment category, primary + follow-up	Surgery only	664	8.9
treatment	RT (+ surgery)	3427	46.2
	RT + CT (+ surgery)	899	12.1
	RT + HT (+ surgery)	914	12.3
	RT + CT + HT (+ surgery)	1351	18.2
	Other/unknown	170	2.3
Follow-up time (years)	< 5	1781	24.0
	5 - 9	1230	16.6
	10 - 14	1036	14.0
	15 - 19	1934	26.0
	20 - 24	993	13.4
	≥ 25	451	6.1

Abbreviations: BC, breast cancer; NKI, Netherlands Cancer Institute; DDHK, Erasmus MC, Daniel den Hoed Cancer Center; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

1981-1986. Median age at breast cancer diagnosis was 50 years. Thirty percent of patients were younger than 45 years at diagnosis, and 6% were younger than 35 years. Median follow-up time was 13.8 years for the entire study population (a total of 87,900 person-years); almost 20% of patients were followed for more than 20 years. Over two-thirds of our study population had surgery plus radiotherapy as primary treatment, and 18% also received adjuvant CT. Twelve percent of the study population was treated by surgery only.

Overall risks of death

In all, 4160 deaths were observed (Table 2.2); by far, the most important cause of death was breast cancer (*n* = 3163, 76% of all deaths). Of these breast cancer deaths, 184 occurred in patients who had developed a contralateral breast cancer during follow-up. Diseases of the circulatory system accounted for 394 deaths, whereas 309 patients died of second malignancies. The 10-year and 25-year actuarial risks of death were as follows: for breast cancer, 34.8% and 49.0%, respectively; for all second cancers (excluding breast), 1.8% and 10.2%, respectively; and for all CVDs (including cerebrovascular accidents), 1.8% and 11.6%, respectively (Figure 2.1).

Table 2.2. Causes of Death in the Dutch Late Effects BC Study

Cause	ICD-9	O (%)	SMR (95% CI)
Infectious diseases	1-139	8 (0.2)	0.96 (0.42-1.90)
Breast cancer (incl. CLBC*)	174	3163 (76.0)	39.4 (38.0-40.8)
Second Malignancies (excl. CLBC*)	140-208, 174 excl.	309 (7.4)	1.16 (1.03-1.29)
Endocrine, nutritional and metabolic diseases	240-279	9 (0.2)	0.22 (0.10-0.42)
Mental disorders	290-319	18 (0.4)	0.83 (0.49-1.32)
Diseases of the nervous system and sense organs	320-389	14 (0.3)	0.64 (0.35-1.07)
Diseases of the circulatory system	410-459	394 (9.5)	0.96 (0.86-1.05)
Cardiovascular disease	410-414; 420-429	269	1.04 (0.92-1.17)
Cerebrovascular accident	430-438	92	0.84 (0.68-1.03)
Diseases of the respiratory system	460-519	62 (1.5)	0.95 (0.73-1.22)
Diseases of the digestive system	520-579	35 (0.8)	0.86 (0.60-1.19)
Diseases of the genitourinary system	580-629	8 (0.2)	0.42 (0.18-0.83)
Miscellaneous diseases†		7 (0.2)	
Ill-defined conditions and unknown	780-799	100 (2.4)	2.70 (2.20-3.29)
External causes of injury and poisoning	800-999	33 (0.8)	1.04 (0.71-1.46)
Complications of treatment		6	
All causes		4160	3.88 (3.76-4.00)

Abbreviations: BC, breast cancer; ICD-9, International Classification of Diseases, 9th revision;
O, observed number of deaths; SMR, standardized mortality ratio.
* CLBC, contralateral breast cancer, defined as the occurrence of a second breast cancer at least 4 months after the first one, on the condition that no distant metastases were manifest up to 6 months after CLBC diagnosis.
† Five diseases of the blood and blood-forming organs (280.0-289.9); two diseases of muscles, bones and connective tissue (710.0-739.9).

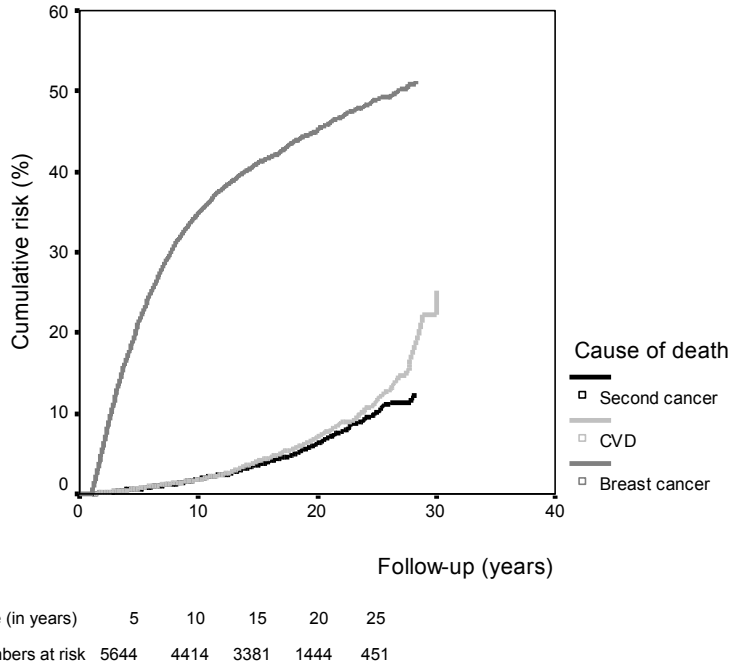


Figure 2.1. Actuarial risks of death from major disease categories

Overall, the study population experienced an almost 4 times higher risk of death from any cause compared with the general population, mainly because of the strongly increased risk of breast cancer death (including CLBC; SMR, 39.4). The contribution of CLBC was moderate with an SMR of 2.29 (95% CI: 1.97 - 2.65) and an AER of 11.8 per 10,000 person-years (Table 2.3). Second malignancies (excluding CLBC) showed a slightly increased SMR of 1.16 (95% CI: 1.03 - 1.29), corresponding with an AER of 4.8. The overall SMRs for vascular diseases were around unity.

During follow-up, the overall AER of death diminished, because of decreasing mortality from breast cancer (Figure 2.2). Yet, throughout follow-up, breast cancer remained the most important cause of death, with AERs of 601, 196 and 135 per 10,000 patient-years in the first 5 years, 10-15 years, and 20-25 years, respectively, after start of treatment. In 25-year survivors, the risk of breast cancer death was 6-fold increased compared to the population, and the AER amounted to 89 per 10,000 patient-years. Of all late breast cancer deaths (>20 years after diagnosis), 30% occurred in patients who developed a CLBC during follow-up, whereas the other 70% died from their primary breast cancer.

The SMR and AER of death from nonbreast second malignancies increased steadily over the years, leveling off after 25 years since start of treatment; for CVD a non-significantly increased risk was found (SMR, 1.50) after 25 years (Figure 2.2, Table 2.4). When age at diagnosis is considered, the SMR for solid tumors was highest among patients who were youngest at first treatment, with SMRs of 1.87 (95% CI: 1.36 - 2.48) for the age group 35-44 years, and 4.37 (95% CI: 2.00 - 8.29) for those <35 years (Table 2.4). The risk of death from CVD was also increased

Table 2.3. Mortality from Second Malignancies

Cause of death	O	E	SMR	95% CI	AER*
All 2nd malignancies (incl. CLBC)	493	347.3	1.42	1.30 – 1.55	16.6
Esophagus	12	5.6	2.14	1.11 – 3.74	0.7
Stomach	19	16.9	1.12	0.69 – 1.76	0.2
Colon, Rectum	47	44.8	1.05	0.77 – 1.40	0.3
Lung	58	33.7	1.72	1.31 – 2.23	2.8
Contralateral breast	184	80.3	2.29	1.97 – 2.65	11.8
Soft Tissue	5	2.0	2.50	0.81 – 5.83	0.3
Melanoma	7	3.6	1.94	0.78 – 4.01	0.4
Cervix	13	7.2	1.81	0.96 – 3.09	0.7
Uterus	7	8.8	0.80	0.32 – 1.64	- 0.2
Ovary	46	26.5	1.74	1.27 – 2.32	2.2
Non-Hodgkin's lymphoma	12	10.1	1.19	0.61 – 2.08	0.2
Leukemia	16	9.1	1.76	1.01 – 2.86	0.8

Abbreviations: O, observed number of deaths; E, expexted number of deaths; SMR, standardized mortality ratio; AER, Absolute excess risk; CLBC, contralateral breast cancer.

* per 10,000 patients per year.

among patients treated before age 45 (SMR = 2.04; 95% CI: 1.26 - 3.12). When considering attained age, we observed trends of declining SMRs for cerebrovascular accidents and solid tumors as patients grew older (*P* for trend <.0001 and <.05, respectively; Table 2.4).

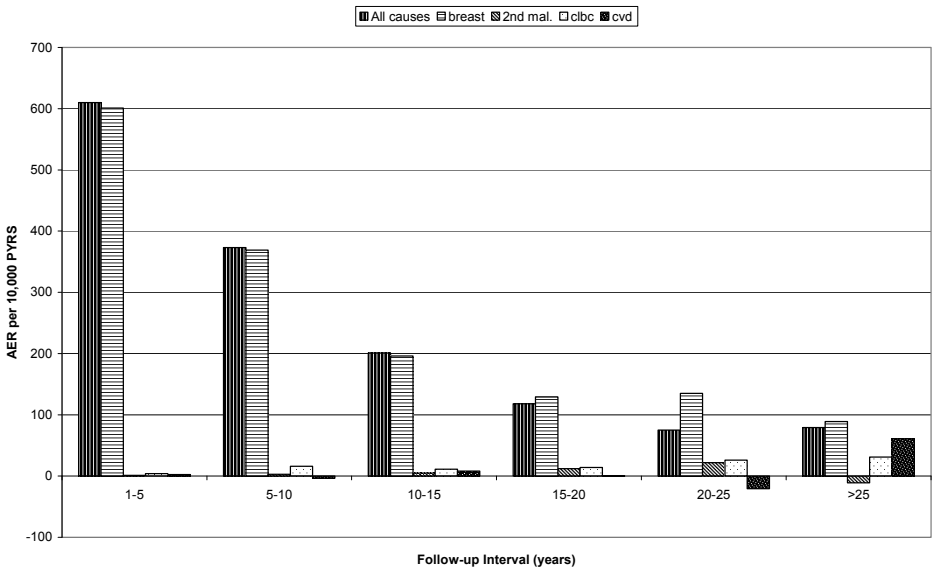


Figure 2.2. Absolute excess risk of death from various disease categories over time, in comparison with the general population. 2nd mal, second non-breast malignancies; clbc, contralateral breast cancer; cvd, cardiovascular disease; AER, absolute excess risk; PYRS, person years.

Table 2.4. Mortality from Second Malignancy and Vascular Disease by Age and Follow-up Interval

	Solid tumors, excl. breast ca				Leukemia, myeloma, lymphoma				Cardiovascular Deaths				Cerebrovascular Deaths			
	O	SMR	95% CI	AER*	O	SMR	95% CI	AER*	O	SMR	95% CI	AER*	O	SMR	95% CI	AER*
Overall	277	1.15	1.02 – 1.29	4.2	32	1.18	0.81 – 1.67	0.6	269	1.04	0.92 – 1.17	1.2	92	0.84	0.68 – 1.03	-2.0
Age at diagnosis																
< 35 years	9	4.37	2.00 – 8.29	13.7	3	1.11	0.23 – 3.25	0.1	21	2.04	1.26 – 3.12	3.9	7	1.56	0.63 – 3.21	0.9
35 – 44 years	46	1.87	1.36 – 2.48	9.5												
45 – 54 years	103	1.31	1.07 – 1.59	7.3	9	1.10	0.50 – 2.08	0.2	60	1.17	0.89 – 1.51	2.6	22	1.18	0.74 – 1.78	1.0
>= 55 years	119	0.88	0.72 – 1.05	-6.2	20	1.23	0.75 – 1.90	1.4	188	0.95	0.82 – 1.10	-3.4	63	0.73	0.56 – 0.93	-8.8
Follow-up interval																
1 – 4 years	44	1.02	0.74 – 1.37	0.3	5	1.09	0.35 – 2.54	0.2	40	1.18	0.84 – 1.61	2.4	11	0.86	0.43 – 1.54	-0.7
5 – 9 years	58	1.05	0.79 – 1.35	1.0	11	1.83	0.92 – 3.28	2.0	42	0.83	0.60 – 1.12	-3.6	23	1.19	0.76 – 1.79	1.5
10 – 14 years	68	1.13	0.88 – 1.43	3.9	9	1.32	0.61 – 2.51	1.1	77	1.26	0.99 – 1.57	8.0	19	0.75	0.45 – 1.17	-3.2
15 – 19 years	64	1.30	1.00 – 1.66	12.4	5	0.86	0.28 – 2.01	-0.7	61	1.01	0.77 – 1.30	0.4	19	0.70	0.42 – 1.09	-7.0
20 – 24 years	37	1.46	1.03 – 2.01	26.0	2	0.51	0.06 – 1.85	-3.5	30	0.77	0.52 – 1.09	-20.6	14	0.74	0.41 – 1.24	-11.0
>= 25 years	6	0.83	0.31 – 1.81	-11.6					19	1.50	0.90 – 2.34	60.9	6	0.95	0.35 – 2.07	-2.9
Attained age																
< 55 years	41	1.68	1.21 – 2.28	5.3	5	2.08	0.68 – 4.86	0.8	10	1.19	0.57 – 2.19	0.5	10	2.38	0.98 – 4.05	1.8
55 – 64 years	74	1.20	0.94 – 1.51	4.4	5	0.82	0.27 – 1.91	-0.4	45	1.38	1.00 – 1.84	4.4	13	1.19	0.64 – 2.04	0.8
>= 65 years	162	1.05	0.90 – 1.23	2.9	22	1.18	0.74 – 1.79	1.2	214	0.98	0.86 – 1.13	-1.2	69	0.73	0.57 – 0.92	-9.0
		$P_{trend} = .01$				$P_{trend} < .60$				$P_{trend} < .10$				$P_{trend} < .0001$		

Abbreviations: O, observed number of deaths; SMR, standardized mortality ratio; AER, absolute excess risk.

* per 10,000 patients per year.

Table 2.5. Mortality from Vascular Disease by type of treatment (primary + follow-up, or primary only*)

	Primary + follow-up treatment (*n* = 7425)			Primary treatment only (*n* = 3854)		
	O	**SMR**	**95% CI**	**O**	**SMR**	**95% CI**
Cardiovascular deaths						
Surgery only	25	0.54	0.35 – 0.80	25	0.56	0.36 – 0.82
RT (± surgery)	169	1.12	0.95 – 1.30	160	1.15	0.98 – 1.35
RT+ CT (± surgery)	21	0.88	0.55 – 1.35	11	1.20	0.60 – 2.14
RT+ HT (± surgery)	27	0.87	0.58 – 1.27	2	1.25	0.15 – 4.52
Cerebrovascular deaths						
Surgery only	15	0.74	0.41 – 1.22	15	0.76	0.42 – 1.25
RT (± surgery)	39	0.60	0.43 – 0.82	36	0.60	0.42 – 0.84
RT+ CT (± surgery)	9	0.98	0.45 – 1.86	5	1.39	0.45 – 3.24
RT+ HT (± surgery)	17	1.34	0.78 – 2.14	-	0	0.00 – 5.27

Abbreviations: O, observed number of deaths; SMR, standardized mortality ratio; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.
*For a subgroup of patients who received only primary treatment.

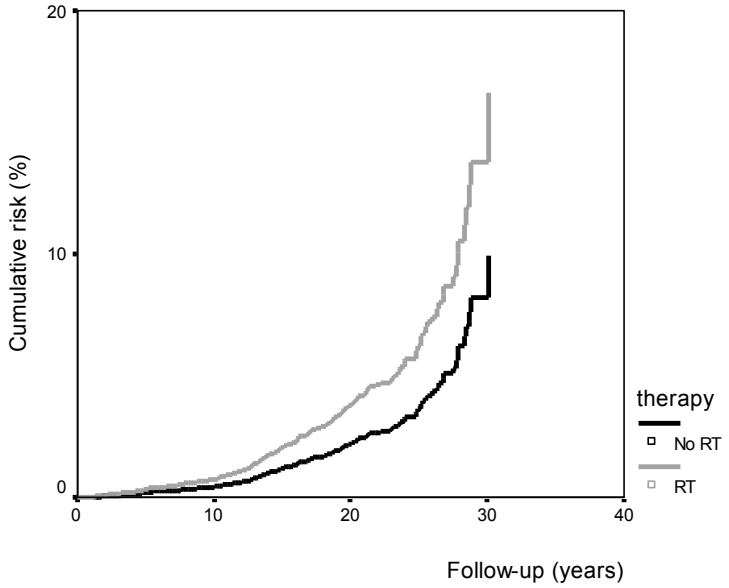
Mortality from CVD in relation to treatment

Patients treated with surgery only had a significantly lower risk of death from CVD than the general population (SMR = 0.54, Table 2.5). For patients treated by RT, mortality from CVD was slightly increased (SMR = 1.12), though not significantly. Nearly identical results were found when the analysis was restricted to patients who received only primary treatment (Table 2.5). We calculated the relative risk (RR) and AER for irradiated patients relative to the nonirradiated group, which resulted in an RR of 2.07 (95% CI: 1.35 - 3.29) and an AER of 18.7 cardiovascular deaths per 10,000 irradiated patients per year. Mortality from CVD was similar for left- and right-sided irradiated patients, with SMRs of 0.99 (95% CI: 0.80 - 1.20) and 1.08 (95% CI: 0.89 - 1.31), respectively.

In Cox model analysis, comparison of cardiovascular mortality between patients treated by RT and by surgery only rendered a hazard ratio (HR) of 1.7 (95% CI: 1.2 - 2.5, adjusted for age and treatment period, Figure 2.3). For patients younger than 50 years at first treatment, the HR associated with RT was further increased (HR = 3.6; 95% CI: 0.9 – 15.0). Although there were some differences in indication for RT fields between the two cancer centers, the RT-related risk of cardiovascular death did not differ by center.

A time-dependent Cox model showed that irradiated patients experienced an increasing risk of cardiovascular death with longer follow-up (HR = 1.0 during the first 10 years of follow-up, and HRs of 1.5 and 2.9 in 10-20 years and more than 20 years after start of treatment, respectively; *P* value for time trend = 0.003). Patients treated in the earlier years (1970–75, 1976–80) experienced an increased risk of death from CVD (HR = 1.3 and 1.5, respectively) compared with patients treated during 1981–1986 (Table 2.6).

During the later years, breast-conserving therapy was used much more frequently. To assess the treatment-related risk with respect to type of radiation treatment, we compared the age-adjusted risk of CVD for patients treated with postmastectomy irradiation, postlumpectomy



time (in years)	5	10	15	20	25
numbers at risk:					
no RT	706	596	476	278	88
RT	4935	3815	2902	1164	360

Figure 2.3. Cox model: risk of death from cardiovascular disease by RT treatment, adjusted for age and treatment period. RT, radiotherapy; HR, hazard ratio.
HR RT vs no RT: 1.74 (95% CI: 1.19 – 2.54)

irradiation, and surgery only from 1979 onward. BCT irradiation was not associated with an increased risk of cardiovascular death in comparison with the control group of surgery only (HR = 1.0; 95% CI: 0.5 – 1.9; Figure 2.4). Patients receiving postmastectomy RT in this period experienced a non-significantly 1.5-fold increased risk of death from CVD.

Mortality from second malignancy in relation to treatment

Significantly increased SMRs were found for esophageal cancer (SMR = 2.14), lung cancer (SMR = 1.72), ovarian cancer (SMR = 1.74) and leukemia (SMR = 1.76; Table 2.3). Although cancers of the esophagus and of connective tissue showed the highest SMRs, their AERs were very low (0.7 and 0.3, respectively) because of the low background mortality in the general population. Lung cancer and ovarian cancer contributed most to the absolute excess mortality with AERs of 2.8 and 2.2, respectively. Patients treated with RT were at elevated risk of death from esophageal cancer (SMR = 2.17), lung cancer (SMR = 2.16), and ovarian cancer (SMR = 2.03; Table 2.7), and also cervical cancer (SMR = 2.31; 95% CI: 1.06 - 4.38) and connective tissue tumors (SMR = 4.51; 95% CI: 1.46 - 10.51). Increased mortality from leukemia was associated most strongly with CT, with an SMR of 5.66 for RT+CT, against an SMR of 1.16 for RT

Table 2.6. Multivariate Cox Regression Analysis for Mortality from Cardiovascular Disease and Solid Tumors, in all patients (n=7425) and in 10-year survivors (n=4414)

All patients	Cardiovascular death		Solid tumors	
Risk Factor	**HR**	**95% CI**	**HR**	**95% CI**
Age at diagnosis*	1.118	1.100 – 1.137	1.033	1.019 – 1.047
Treatment period: vs 1981 - 1986				
1970 – 1975	1.34	0.93 – 1.92	1.30	0.94 – 1.79
1976 - 1980	1.54	1.11 – 2.14	1.25	0.90 – 1.74
Type of treatment: vs surgery only				
RT	2.03	1.33 – 3.10	1.36	0.94 – 1.97
RT + CT	1.47	0.80 – 2.67	0.84	0.51 – 1.39
RT + HT	1.70	0.99 – 2.93	0.41	0.20 – 0.84

10-year survivors	Cardiovascular death		Solid tumors	
Risk Factor	**HR**	**95% CI**	**HR**	**95% CI**
Age at diagnosis*	1.108	1.087 – 1.130	1.020	1.003 – 1.038
Treatment period: vs 1981 - 1986				
1970 - 1975	1.38	0.89 – 2.14	1.19	0.77 – 1.84
1976 - 1980	1.62	1.07 – 2.46	1.40	0.92 – 2.14
Type of treatment: vs surgery only				
RT	2.08	1.25 – 3.47	1.57	0.98 – 2.54
RT + CT	2.38	1.18 – 4.77	1.34	0.70 – 2.53
RT + HT	2.42	1.27 – 4.61	0.68	0.29 – 1.61

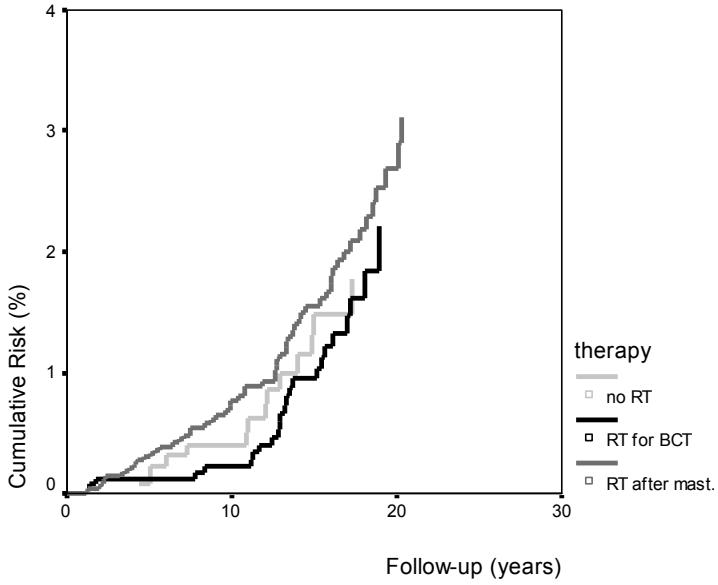
Abbreviations: HR, hazard ratio; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

* Continuous term.

only (RR for RT+CT vs. RT = 4.89; 95% CI: 0.79 - 22.9). With regard to solid tumors, we did not find any indication for an association of RT+CT with increased mortality in comparison with RT only (SMRs, 0.87 and 1.29, respectively, Table 2.7); a separate analysis in 10-year survivors showed similar results (HR = 1.34 for RT+CT, against 1.57 for RT, Table 2.6) .

Discussion

In this large, long-term follow-up study of breast cancer patients with near complete information on cause of death, the most pronounced excess risk of death was found for breast cancer itself, with 350 excess deaths per 10,000 patients per year. During follow-up, the relative risk of death from breast cancer declined, but even after more than 25 years since first treatment, patients still experienced a 6-fold increase of breast cancer mortality. Contrary to our expectations, overall cardiovascular mortality was not increased in our study population compared with the general population (SMR = 1.0). However, when we compared irradiated with nonirradiated patients within the cohort, adjusting for age and treatment period, RT



time (in years)	5	10	15	20
numbers at risk:				
no RT	331	269	199	40
RT for BCT	1475	1254	930	97
RT after mast.	1558	1162	886	240

Figure 2.4. Cox model: risk of death from cardiovascular disease by treatment modality, adjusted for age, for patients treated since 1979. RT, radiotherapy; BCT, breast conserving therapy; mast., mastectomy; HR, hazard ratio.
HR RT for BCT vs no RT: 0.96 (95% CI: 0.49 – 1.89)
HR RT after mast. vs no RT: 1.52 (95% CI: 0.85 – 2.71)

Table 2.7. Mortality from Second Malignancies by type of treatment (primary + follow-up)

	Solid Tumors (excl. breast ca)			Esophagus			Lung			Ovary			Leukemia		
	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI	O	SMR	95% CI
Surgery only	34	0.92	0.64 - 1.29	1	1.02	0.03 - 5.69	5	1.05	0.34 - 2.46	5	1.29	0.42 – 3.02	2	1.22	0.15-4.43
RT (± surgery)	175	1.29	1.11 - 1.50	7	2.17	0.87 - 4.47	41	2.16	1.55 - 2.93	30	2.03	1.37 – 2.89	6	1.16	0.43-2.52
RT+ CT (± surg.)	30	0.87	0.59 - 1.24	2	5.36	0.65 - 19.37	4	1.26	0.34 - 3.23	7	3.74	1.51 – 7.71	3	5.66	1.17-16.5
RT+ HT (± surg.)	10	0.36	0.17 - 0.66	2	3.29	0.40 - 11.90	4	1.17	0.32 - 3.01	1	0.32	0.01 – 1.77	3	2.80	0.58-8.19

Abbreviations: O, observed number of deaths; SMR, standardized mortality ratio; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

was associated with a significant 1.7-fold increased risk of cardiovascular death. In absolute terms, irradiated patients experienced 19 excess deaths from CVD per 10,000 patient-years. Postmastectomy RT showed a 2-fold increased cardiovascular mortality when applied before 1979, consistent with the literature on older radiation techniques, and then a decline in risk to an HR of 1.5 (95% CI: 0.9 – 2.7) when applied from 1979 on. For BCT irradiation administered

in the latter period, we did not find an association with increased risk of cardiovascular death (HR for BCT vs. surgery only = 1.0; 95% CI: 0.5 - 1.9).

Second malignancies (excluding CLBC) showed a slightly though significantly increased SMR of 1.16, corresponding with 5 excess deaths per 10,000 patient-years. CLBC contributed to only a small proportion (6%) of all breast cancer deaths, with 12 excess deaths per 10,000 patient-years. However, the AER for death from CLBC increased steadily through follow-up from 4 in the 1–5-year interval up to 31 in 25-year survivors. We cannot conclude from the present data whether the excess risk was associated with treatment; in the near future, we will report on this issue in a related paper on the incidence of second malignancies.

When interpreting our results with regard to second cancer risk, the effect of factors other than treatment should be considered.[36] For example, for ovarian cancer, which showed stable SMRs throughout follow-up, rendering a treatment-related cause unlikely, the increased mortality is more likely due to a common hormone-related etiology and/or genetic predisposition. For lung cancer, however, RT is the most plausible explanation for the increased mortality, as demonstrated by an increasing ratio of SMRs over time when comparing irradiated with nonirradiated patients (RR, 1.5 in the 1–10-year interval, to 3.6 in >20 years of follow-up). The mortality increase from esophageal cancer over time (SMRs of 1.8 after 5–10 years and 4.3 after 20–25 years) is also likely due to RT. These findings are in line with results reported previously.[11,20-22,37,38] With regard to leukemia, the elevated risk was associated with the administration of CMF added to RT (SMR = 5.7), as has been described by others before.[27,28] Mortality from solid tumors was most strongly increased in patients treated before the age of 35 (SMR = 4.4). With aging of the young patient cohort, the elevated risks disappeared. The reason for this decline is unclear. Possibly, patients who are younger at the diagnosis of breast cancer have a genetic predisposition for developing other malignancies at an early age, or have a greater sensitivity to the development of treatment-associated malignancies.

Our observation that CVD mortality increased over time in irradiated patients corresponds with the literature[5,6,18,39-40] and is assumed to be the result of a long induction period. The cardiac injury caused by radiation is thought to be mediated by damage of the vascular endothelium, leading to accelerated atherosclerosis and, in the long term, to an increased risk of vascular stenosis and thromboembolism of the arteries of the heart muscle.[41] In studies by Gyenes et al.[42] and Paszat et al.,[16] cardiac mortality was associated with a higher irradiated heart volume and a higher fraction size, respectively. As for solid tumors, we observed a declining trend of SMR for CVD with advancing age at start of first treatment. Among patients treated before age 45, the SMR was 2.0, whereas SMRs of 1.2 and 0.95 were found in patients first treated at ages 45-54 and 55 or older, respectively. The decrease of SMRs with increasing age may be due to the strong increase in baseline risk with advancing age in the general population. However, also in the direct comparison of irradiated with non-irradiated patients, the relative risks were highest in young patients, indicating that they are at greater risk for cardiac effects of radiation.

In many studies on RT-related cardiovascular mortality, the risk between left- and right-sided tumors is compared, as a surrogate for cardiac exposure to radiation.[15-18] Whether it is useful to analyze by laterality depends on the fields used in the patient population. In the last update of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on local therapy by Peto,[43] comparison of cardiovascular mortality between patients treated with RT and without RT rendered a rate ratio of 1.26 (2p = .00002), mainly because of regimens that irradiated the IMC field.

In case of irradiation of the IMC via a direct anterior field, the heart and coronary arteries are exposed to a dose quite similar for the left- and right-sided field. In our study, where many patients received radiation to the IMC by the anterior field, we indeed found no difference in risk between left and right-sided tumors.

Recent studies on cardiovascular risk following postlumpectomy RT according to laterality show inconsistent results. This may partly be explained by the types of RT fields used. Rutqvist et al.[14] and Vallis et al.,[17] who reported on CVD incidence as well as mortality, did not find excess risk of CVD among patients treated to the left breast, with regional nodal areas irradiated in only 12% and <6% of the patients, respectively. In the study by Nixon et al.,[15] 80% of the patients received regional node treatment, including the ipsilateral IMC, using deep tangential fields. Although these fields would be expected to deliver an increased dose of radiation to the heart for left-sided tumors as compared with right-sided tumors, left- vs. right-sided irradiation was not associated with an increased risk of cardiac mortality. The number of cardiac events was small, however, and a maximal follow-up time of 12 years was probably too short to demonstrate increased CVD mortality. Paszat et al.[16] and Darby et al.,[18] on the other hand, presented in two large population-based studies significantly increased risk estimates of cardiac death for left-sided tumors (2.1 and 1.1, respectively). In the population-based study by Giordano et al.,[40] a statistically significant increase for left-sided tumors was found only in patients treated between 1973 and 1979 (HR for 1979 = 1.5), whereas after 1979 the difference in risk between patients with left-sided and right-sided tumors declined and was no longer statistically significant. In the last three studies, no information was available on the proportion of patients receiving radiation treatment to the regional nodes.

Instead of comparing patients with left-sided and right-sided tumors, Højris et al.[13] investigated in the Danish Breast Cancer Cooperative Group 82b and 82c trials the risk of ischemic heart disease, comparing patients treated between 1982 and 1990 with or without postmastectomy radiation. All irradiated patients received RT to the chest wall field and regional lymph nodes, including the ipsilateral IMC field. After 12 years, no increased risk of ischemic heart disease was found among the patients who received radiation (HR = 0.84; 95% CI: 0.4 - 1.8). However, with just over 3,000 patients, this was a relatively small study, and follow-up time may have been too short to draw firm conclusions. In our own study, we collected only information on RT fields in 10-year survivors. In a forthcoming paper, we will evaluate the

incidence of CVD specifically in relation to the different types of radiation fields used in this subgroup of over 4,000 patients.

We observed in the current study that cardiovascular mortality among nonirradiated patients was lower than in the general population. Similar results have been reported by others. Cuzick et al.[5] reported a decreased SMR of 0.69 for CVD in nonirradiated patients, and Ederer et al.[44] reported ratios for CVD overall varying between 0.63 and 0.80. These studies did not offer a plausible explanation for the decreased risk, but we think there is a biologic explanation for this phenomenon. First, the risk profile for breast cancer (e.g. late menopause) may be protective against CVD. In addition, women may well opt for a healthier lifestyle after breast cancer diagnosis, which would reduce their risk of CVD. Finally, particularly in this hospital-based study population, we may have selected breast cancer patients with higher socioeconomic status, which has been described to be associated with lower rates of CVD.

To rule out the possibility that the lower than expected number of CVD deaths was due to misclassification of cause of death in patients who suffered from recurrent disease, we analyzed CVD mortality by treatment in the subgroup of patients that did not develop breast cancer recurrences during follow-up. The results from this analysis were almost identical to those in the complete cohort (Table 2.5), supporting the finding that breast cancer patients treated by surgery only indeed are at lower risk of developing CVD compared to the general population.

When interpreting our results, the strengths and limitations of our study should be considered. Unlike most other studies, ours included detailed information on all primary and follow-up treatments administered to the study population. Our follow-up is long and almost complete. We obtained validation for 95% of second malignancies through pathology reports. Cardiovascular disease, however, was not always reported to the cancer clinic, and many of our patients died a long time after their last oncologic follow-up. To avoid underreporting of cardiovascular death, we went through the labor-intensive process of mailing thousands of questionnaires to general practitioners for completion of medical information. The characteristics of patients with missing information, after all tracing efforts (6%), were very similar to those of patients with complete follow-up. For ascertainment of the cause of death, we used the same coding rules that Statistics Netherlands uses to record the underlying cause of death. However, in addition to the common death certificate information, we used information also from medical records, medical letters, and follow-up information from general practitioners, which has likely led to an even more valid cause of death. Misclassification of certain causes of death could result in underestimation or overestimation of risks. It seems unlikely, however, that such misclassification would differ between treatment groups.

In a retrospective study, one should always consider potential confounding by indication. In both cancer centers, indications for RT fields and CT regimens were specified in a treatment protocol to which all clinicians closely adhered (as evident from descriptive analyses of primary treatment according to stage; data not shown). Treatment in the period under study

was affected by neither socioeconomic status, distance to the cancer center, nor the presence of cardiovascular disease, as illustrated by the fact that among patients at high cardiovascular risk (i.e., with a history of CVD or known hypertension at the time of breast cancer diagnosis [*n* = 528]), 95.0% with an indication for RT (axillary node involvement and/or medially located tumor) were indeed irradiated, as compared with 95.1% among low-risk patients (no CVD risk factors at breast cancer diagnosis). In other words, the baseline risk of CVD did not differ in the irradiated and nonirradiated patients.

An inherent limitation of retrospective cohort studies evaluating long-term treatment effects is the evolution of treatment during the study period. For example, ^{60}Co was still used in the study period in approximately 30% of the patients. Complete replacement by high-energy linear accelerators since then has resulted in a more homogeneous dose distribution. Shielding is more accurate nowadays, and the dose given per fraction is lower, resulting in less toxicity. Also, the indication for the IMC field has changed, partly because of a growing awareness of the possible cardiovascular risk imposed by adjuvant RT. The risk reduction expected from these improvements will have to be studied in the future.

In conclusion, our results have implications for breast cancer patients treated in the past and for currently treated patients. A large number of breast cancer patients treated with older RT methods are alive today and remain at risk for death from CVD. Those treated at a young age may be especially at risk for CVD morbidity and mortality. Timely intervention in other risk factors of CVD (e.g. smoking, hypertension, obesity) may help to reduce the absolute excess risk of CVD in these breast cancer survivors.

When considering the relevance of our findings for the current patient population, it is reassuring that even after a median follow-up of over 15 years, there is no indication of increased cardiovascular mortality after BCT. However, we must take into account that the absence of raised risks of death does not preclude increased incidence of disease, because it may take years before CVD results in death. Furthermore, we should realize that many patients are still being treated by mastectomy plus adjuvant RT. Especially for younger patients, there is a reverse trend from BCT back to mastectomy, because of their higher risk of breast cancer recurrence. According to our data, postmastectomy RT after 1979 was associated with nonsignificantly increased mortality from CVD. Continued follow-up of patients treated from the late 1980s on will be necessary to evaluate whether the benefits from RT with respect to reduction of local recurrence and breast cancer mortality rates will not be offset by long-term excess mortality from other diseases.

Acknowledgment

We thank E.K. Adriaans, M.L.R. Beelen, A.W. van den Belt-Dusebout, V.B. Hartog, S.E. Kraus, R. Noyon, A.M.G. van de Swaluw, and the hospital cancer registries of the Netherlands Cancer

Institute and the Daniel den Hoed Cancer Center for assistance in data collection, and W.J. Klokman for statistical advice on the person-year-analysis program.

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3 Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer

Maartje J. Hooning, Berthe M.P. Aleman, Michael Hauptmann, Margreet H.A. Baaijens, Jan G.M. Klijn, Ruth Noyon, Marilyn Stovall, Flora E. van Leeuwen

Submitted

Abstract

Purpose

To assess long-term risk of contralateral breast cancer (CBC) in a predominantly young breast cancer (BC) population, focusing on the effects of different radiation regimens, chemotherapy and family history of BC.

Methods

We studied incidence of CBC in 7221 1-year survivors of BC who were treated between 1970 and 1986. Treatment-specific risk of CBC was compared with general population rates and evaluated in Cox proportional hazards regression models.

Results

After a median follow-up of 14 years 503 CBCs were observed (standardized incidence ratio = 2.9; 95% CI: 2.7 - 3.2), implying 46 excess cases per 10,000 patient-years. RT-associated risk of CBC increased with decreasing age at first treatment (for age<35: hazard ratio [HR] = 1.78; 95% CI: 0.85 - 3.72; for age>45: HR = 1.09; 95% CI: 0.82 - 1.45). Postmastectomy RT using direct electron fields led to a significantly lower radiation-exposure to the contralateral breast than postlumpectomy RT. Women treated before age 45 with postlumpectomy RT experienced 1.5-fold (95% CI: 1.11 - 2.09) increased risk of CBC compared with those who had postmastectomy RT. The joint effects of postlumpectomy RT and positive family history for BC on risk of CBC were greater than expected when individual risks were summed (HR = 3.31; 95% CI: 1.96 - 5.60; *P* for departure from additivity = 0.045). The medial part of the contralateral breast received a higher mean dose (3.8 Gy) than the lateral part (1.3 Gy). RT-associated risk of medially located CBC in patients treated before age 45 showed a dose-response relationship (linear excess relative risk/Gy = 0.37; *P* for trend = 0.01). Treatment with adjuvant chemotherapy (cyclophosphamide, methotrexate and fluorouracil) was associated with a non-significantly decreased risk of CBC in the first 5 years of follow-up, but did not reduce CBC risk in subsequent years.

Conclusions

Young BC patients treated with postlumpectomy RT experience increased risk of CBC, especially in case of a positive family history of BC. This finding should be taken into account when advising breast-conserving therapy in young BC patients, particularly in mutation carriers, and warrants further research.

Introduction

Women with breast cancer have a 3- to 4-fold increased risk of developing a new primary cancer in the contralateral breast, as compared to the risk of a first primary breast cancer among other women.[1,2] The excess risk can be largely explained by a common etiology, e.g., through genetic predisposition and/or hormonal risk factors.[3-8] Still, treatment-related causes may play a role as well. Boice et al. estimated in 1992 that 11% of all CBCs in women irradiated before age 45 could be attributed to RT.[9] However, radiation techniques evaluated in their study are no longer routinely used and only few studies have examined whether RT as applied from the 1980s onwards affects the risk of CBC.[5,6,10-13] So far, results are inconclusive, and hardly no distinction has been made between specific RT regimens such as postlumpectomy and postmastectomy RT that may lead to a different radiation exposure of the contralateral breast. Some studies have provided evidence that adjuvant chemotherapy (CT) may reduce the risk of CBC, either through induction of premature menopause or through killing of tumor cells in the contralateral breast.[3,5,14,15] This further complicates analysis of potential risk factors, especially in younger patients where CT and RT are expected to have more – if any – effect.[8,16-19]

A positive family history of BC is an established risk factor for CBC. Because several breast cancer susceptibility genes play a role in the DNA damage repair pathway, it has been speculated that young patients with a strong family history of BC are more susceptible to radiation-induced CBC than young patients without a family history. However, this issue has been hardly addressed. The purpose of our study is to determine risk for CBC in a large BC cohort with long-term and near complete follow-up, focusing on the influence of relatively modern BC treatments given to a predominantly young BC population. We also assessed the effects of smoking and family history, as well as potential interaction of family history with treatment.

Patients and methods

Data collection procedures

The Late Effects BC cohort consists of 7425 1-year survivors, age below 71 at diagnosis, treated for Stage I, II and IIIA female breast cancer in the period 1970-1986 in the Netherlands Cancer Institute (NKI) or the Erasmus MC, Daniel den Hoed Cancer Center (DDHK). A detailed description of data collection procedures has been published previously.[20] In brief, all patients were identified through the hospital-based cancer registries of the two centers. From the registries and the patient records we collected date of BC diagnosis, tumor histology, axillary lymph node involvement, dates and treatments of primary BC and of recurrent disease (type of surgery, radiation fields, chemotherapy, hormonal treatment), date and diagnosis of contra-

lateral breast cancer (CBC), information on family history of (breast) cancer in first and second degree relatives, smoking habits, date of most recent medical information or date of death. For a subgroup of patients, who were treated at the NKI before age 45 years (n = 1044), we could obtain information on the quadrant where the contralateral breast cancer was located. For this group we also collected detailed information on RT regimen (field configuration, radiation technique, total dose and fractionation schedule). Information on smoking habits was obtained from the patients' general practitioners both at the date of diagnosis of BC and at the end of follow-up. Patients were considered as continuous smokers if they were smokers at the end of follow-up or had stopped smoking less than one year before the end of follow-up.

Patients who had been irradiated above the diaphragm or treated with CT before the diagnosis of breast cancer were excluded from the study population. For the present analysis, we also excluded patients with previously diagnosed breast cancer or synchronous bilateral breast cancer, defined as a contralateral BC diagnosed within 4 months of the primary BC, thus reducing the study population to 7221 patients.

Special attempts were made to establish the medical status of patients lost to follow-up at the two institutes by mailing a questionnaire to specialists in other hospitals and to general practitioners. Complete follow-up information until at least January 1st, 2000 was eventually available for 94% of all patients. For 95% of all CBCs we obtained confirmation through pathology reports.

Treatment

During the 1970s, standard treatment for Stage I, II and IIIA breast cancer was modified or radical mastectomy with or without RT. As of 1975 adjuvant systemic treatment was introduced for node-positive patients: combination chemotherapy for premenopausal patients, and, gradually from 1980 onwards, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of CMF (cyclophosphamide, methotrexate and fluorouracil) during the whole study period; until 1980 12 cycles were administered, afterwards only 6. In 1980 breast conserving therapy was introduced in both hospitals, consisting of wide local excision and axillary lymph node dissection, followed by whole breast irradiation.[21]

The radiotherapy regimen depended on type of surgery and stage of disease. In both institutes, irradiation of the ipsilateral internal mammary chain (IMC) field was common for patients with centrally or medially located tumors and/or axillary lymph node metastases. In case of extensive axillary nodal metastases, the axilla and supraclavicular nodes were irradiated as well. Chest wall irradiation was given in case of an incomplete resection or an extensive primary tumor. The dose to the IMC varied from 40 Gy in 15 fractions in 3 weeks to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and electrons; the chest wall received doses between 35 Gy and 45 Gy in 15 to 20 fractions, using a direct electron field. Breast irradiation consisted of a dose of 50 Gy in 25 fractions using two tangential

photon beams (4-8 MV or cobalt-60), followed by a boost of 15-25 Gy to the tumor bed, often using an iridium implant. Alternatively, especially if an implant was technically not feasible, an electron boost was given.

Dosimetry

Patients received radiation therapy by means of external beam therapy with or wthout interstitial brachytherapy. Absorbed dose to the contralateral breast from external beams is a combination of radiation directly from the primary beam, scatter off the collimators and filters, and leakage through the head of the machine. Radiation equipment and techniques changed considerably over the years. For the calculation of the individual radiation doses to the contralateral breast we needed not only information on the irradiated regions, but also on the specific regimens used. Although the regions irradiated were known for each patient, the RT regimens were only available for the patients treated at the NKI before the age of 45 years (n = 1044), which made dosimetry possible for this subgroup. Dose estimations to the contralateral breast for various radiotherapy regimens (n = 31) were performed by one of the authors (M. Stovall) in Houston, TX, USA, at the Department of Radiation Physics of the M.D. Anderson Cancer Center, University of Texas. For each specific radiotherapy regimen, we determined the field configuration, tumor dose, use of wedge filter or beam blocking, and radiation energy. Dose estimates were derived from measurement in tissue-equivalent phantoms, molded on women in treatment positions.[22] Doses were measured for tangential breast fields, IMC fields, chest wall fields, supraclavicular and axillary fields, and for internal or external boosts to the breast. With respect to brachytherapy, doses to the contralateral breast were calculated using treatment planning data in clinical use.[23] The two implant locations selected for dosimetry were the upper outer quadrant and the areola since these areas usually have sufficient breast tissue available for an implant.
Dose estimates were produced for all four quadrants and the central area of the contralateral breast.

Statistical analysis

We compared the incidence of CBC in the study population with BC incidence in the Dutch female population. In this person-years type of analysis, the ratio of the observed (O) and expected (E) numbers of BC in the study population was determined taking into account the person-years of observation in the cohort (by age and calendar period). We used breast cancer incidence rates from the Eindhoven Cancer Registry up to 1990[24,25] and from the Netherlands Cancer Registry for the period of 1990 to 2000 as reference rates.[26-28] Cancer incidence data for the whole country were not available for the total study period. We defined a CBC as a second primary cancer in the contralateral breast of any invasive histological type, diagnosed at least 4 months after the first breast cancer, with no signs of distant disease up to 6 months after the date of CBC. Time at risk began 1 year after the start of first treatment and ended at

the date of diagnosis of CBC, date of treatment for advanced disease (since CBCs by definition could not occur after distant metastasis had been diagnosed), date of death or date of most recent medical information, whichever occurred first. The confidence limits of the O/E ratio or standardized incidence ratio (SIR) were obtained using exact Poisson probabilities of O numbers.[29] O/E ratios were calculated for all BC patients together and separately by follow-up interval, type of treatment, age at first treatment, and attained age. Absolute excess risk (AER) was calculated by subtracting the expected number of cases from the number observed, and dividing by person-years at risk (expressed per 10,000 person-years).

Cumulative (actuarial) probabilities of CBC were estimated as a function of time since initial treatment using the Kaplan-Meier method. The Cox proportional hazards model[30] was used to quantify the effects of different treatments on CBC risk taking into account several covariates (age at first treatment, smoking habits, family history of cancer). Time since breast cancer diagnosis was used as time scale. We evaluated the effect of radiotherapy and chemotherapy on risk of CBC by follow-up time in time-dependent Cox models.

Biological interaction was evaluated as departure from additivity of the effect of two risk factors, where the 'interaction risk' is the risk that cannot be explained by the joint exposure to both risk factors, as expressed in the following formula[31]:

$^{1}R_{INT} = R_{A+B} - (R_A + R_B - R_U)$.

We performed statistical analysis to determine whether the joint effect was different from that of a single factor. The test was based on the null hypothesis $\gamma=0$ in $R_{A+B} = (R_A + R_B - R_U + \gamma)$, i.e., allowing for an additive departure (γ) from an additive joint effect. The test was a two-sided likelihood ratio test.

Person-years analyses and Cox's models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL). EPICURE software[32] was used for the tests on departure from additivity.

Results

Table 3.1 shows the general characteristics of the study population. Median age at BC diagnosis was 50 years. Thirty percent of patients were younger than 45 years at diagnosis, and 6% were younger than 35 years. Almost 20% of patients were followed for more than 20 years. The use of breast conserving therapy considerably increased during the study period, from 6% during the years 1970-1979 to 45% in the period 1980-1986. Information on smoking habits was available for 58% of patients: 55% of these had never smoked, 37% smoked at the time of BC diagnosis, while 10% still smoked at the end of follow-up (Table 3.1). Sixteen percent of patients reported family members (first or second degree) known with breast

1. A, B are risk factors; R_{INT} is interaction risk; R_U is background risk.

Table 3.1. Characteristics of the Dutch Late Effects BC Study

Characteristic		No. of BC patients	%
No. of patients		7221	100
Hospital	NKI	3209	44.4
	DDHK	4012	55.6
Age at BC diagnosis (years)	< 35	456	6.3
	35 - 39	710	9.8
	40 - 44	1039	14.4
	45 - 54	2568	35.6
	≥ 55	2448	33.9
Year of first treatment of BC	1970 - 79	3323	46.0
	1980 - 86	3898	54.0
Axillary node involvement (at diagnosis)	Node negative	3397	47.0
	Axillary node pos., subclav. neg.	3095	42.9
	Subclav. pos.	576	8.0
	Unknown	153	2.1
Laterality	Left	3766	52.2
	Right	3455	47.8
Treatment category*	Surgery only	810	11.2
	RT (+ surgery)	4989	69.1
	RT + CT (+ surgery)	1133	15.7
	RT + HT (+ surgery)	77	1.1
	RT + CT + HT (+ surgery)	162	2.2
	CT and/or HT (+ surgery)	50	0.7
Primary radiation: type of treatment	Postmastectomy RT	4357	60.3
	Postlumpectomy RT	1726	23.9
	RT for patients with positive subclavicular lymph nodes	234	3.2
	No RT	904	12.5
Follow-up time (years)	< 5	1749	24.2
	5 - 9	1202	16.6
	10 - 14	1045	14.5
	15 - 19	1883	26.1
	20 - 24	933	12.9
	≥ 25	409	5.7
Family history of (breast) cancer	Negative	1651	22.9
	Positive for cancers other than BC, in < 3 relatives	1169	16.2
	Positive for cancers other than BC, in >= 3 relatives	618	8.6
	Positive for BC, in < 3 relatives	870	12.0
	Positive for BC, in >= 3 relatives	283	3.9
	Unknown	2630	36.4

Abbreviations: BC, breast cancer; NKI, Netherlands Cancer Institute; DDHK, Erasmus MC, Daniel den Hoed Cancer Center; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

*Treatment received until distant recurrence.

Table 3.1. (continued) Description of smoking habits

Risk factor		No. of BC patients	%
Smoking:	Never	2319	32.1
	Unknown at BC diagnosis, but not at end of follow-up	327	4.5
	Smoking at BC diagnosis, but not at end of follow-up	402	5.6
	Smoking at BC diagnosis, unknown at end of follow-up	732	10.1
	Smoking through the end of follow-up	433	6.0
	Unknown	3008	41.7

Abbreviations: BC, breast cancer.

cancer at the time of their own first BC diagnosis; 4% had 3 or more relatives affected (Table 3.1). Distribution of average breast dose to CBC, received by quadrant, as estimated using the Stovall model for different RT regimens is presented in Figure 3.1. Highest dose was observed from postlumpectomy RT with breast tangentials and from IMC RT using ^{60}Co (1.2 – 3.6 Gy and 1.0 – 3.3 Gy, respectively); somewhat lower doses were seen for tangentials using linear accelerators and for a boost with ^{60}Co (0.6 - 1.4 Gy and 0.5 – 1.4 Gy, respectively). Irradiation of chest wall or IMC with electrons yielded a much lower dose to the CBC, ranging from 0.04 to 0.3 Gy. Depending on the type of energy used for tangentials and boost, the average radiation dose to the contralateral breast added up to 3.8 – 4.6 Gy (from ^{60}Co) or 1.6 – 2.9 Gy (from high energy photons) for the inner quadrants, and to 1.2 – 1.4 Gy (from ^{60}Co) or 0.6 – 1.1 Gy (from high energy photons) for the outer quadrants.

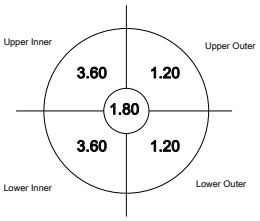
Risk of CBC by follow-up interval and age

After a median follow-up of 13.8 years (range 1.0 – 33.0 years) 503 events of CBC were observed in the study population, resulting in a significantly increased SIR of 2.91 compared to the general female population (Table 3.2) and an AER of 46.1/10,000 person-years. Median time to CBC was 7.7 years (range 1.0 – 27.3 years). The actuarial risks of CBC at 10, 20 and 30 years were 6.5%, 12.3% and 17.1%, respectively.

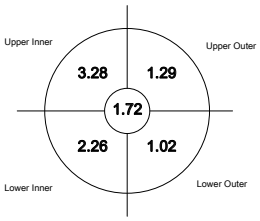
The SIR for CBC decreased with follow-up duration (Table 3.2), from 3.84 for 1-4 years since first treatment, to 1.89 after 20 years (*P* for trend <0.001), corresponding with AERs of 53.1 and 29.9/10,000 patient-years, respectively.

The risk of CBC was highest among patients who were youngest at first treatment, with SIRs of 5.18 for the age group of 35-39 years, and 8.46 for those < 35 years (Table 3.2). Attained age showed the same pattern, with a SIR of 9.84 for developing CBC below age 45, and declining SIRs as patients grew older (*P* for trend <0.001).

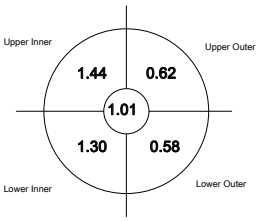
Dose to contralateral breast from tang. breast RT
(50 Gy with Co60)



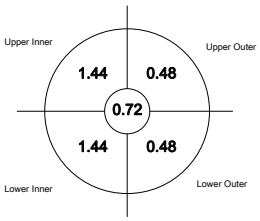
Dose to contralateral breast from IMC-RT
(50 Gy with Co60)



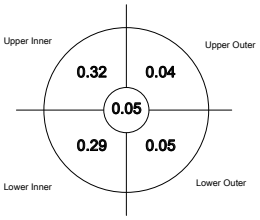
Dose to contralateral breast from tang. breast RT
(50 Gy with 6-8 MeV)



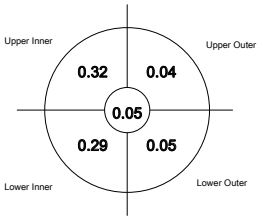
Dose to contralateral breast from boost
(20 Gy with Co60)



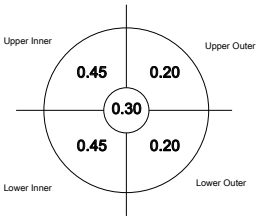
Dose to contralateral breast from chest wall RT
(40 Gy with electrons)



Dose to contralateral breast from IMC-RT
(40 Gy with electrons)



Dose to contralateral breast from boost
(25 Gy with Iridium implant to areola)



Dose to contralateral breast from boost
(25 Gy with electrons)

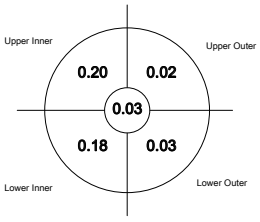


Figure 3.1. Average dose (Gy) to quadrants of the contralateral breast by different fields and beam types

Risk of CBC in relation to treatment and other risk factors

Overall, multivariate Cox model analysis of potential risk factors for CBC showed an RT-associated risk of 1.15 (95% CI: 0.89 - 1.50, Table 3.3). In patients irradiated before age 35 years the HR was 1.78 (95% CI: 0.85 - 3.72), while for patients irradiated at 45 years or older risk decreased to 1.09 (95% CI: 0.82 - 1.45, Table 3.3). Persistent smoking until the end of follow-up

Table 3.2. Risk of Contralateral Breast Cancer by Follow-up interval, Age at start of treatment, and Attained age

	Risk of CBC				
	O	**E**	**SIR**	**95% CI**	**AER***
Overall	503	173.0	2.91	2.66 – 3.18	46.1
Follow-up interval					
1 – 4 years	157	40.9	3.84	3.27 – 4.49	53.1
5 – 9 years	155	45.4	3.41	2.90 – 4.00	54.3
10 – 14 years	104	43.6	2.39	1.95 – 2.89	37.8
15 – 19 years	60	28.9	2.08	1.58 – 2.67	33.0
>= 20 years	27	14.3	1.89	1.25 – 2.75	29.9
			$P_{trend} < 0.001$		
Age at start of treatment					
< 35 years	40	4.7	8.46	6.04 – 11.5	84.8
35 – 39 years	65	12.5	5.18	4.00 – 6.61	73.5
40 – 44 years	82	24.7	3.32	2.64 – 4.12	50.2
45 – 54 years	186	68.4	2.72	2.34 – 3.14	42.6
>= 55 years	130	62.5	2.08	1.74 – 2.47	31.7
			$P_{trend} < 0.001$		
Attained age					
< 45 years	68	6.9	9.84	7.65 – 12.5	82.0
45 – 54 years	148	37.9	3.90	3.30 – 4.59	57.6
55 – 64 years	146	57.9	2.52	2.13 – 2.97	38.4
>= 65 years	141	70.3	2.01	1.69 – 2.37	31.8
			$P_{trend} < 0.001$		

Abbreviations O, observed number of events; E, expected number of events; SIR, standardized incidence ratio.
*AER, absolute excess risk per 10,000 patients per year.

was associated with an increased risk of CBC in comparison with non-smoking (HR = 1.53). A positive family history of cancer was also a significant risk factor for developing CBC. Patients with 3 or more relatives with BC experienced the highest risk, with a HR of 2.39 (95% CI: 1.67 - 3.44), compared to patients with no affected relatives.

Subsequently, we analyzed risk of CBC by type of RT regimen in patients < 45 years at first treatment (Figure 3.2). Patients treated with postlumpectomy RT had a significantly 1.5-fold increased risk of CBC when compared with patients treated with postmastectomy RT, while the latter group did not experience increased risk of CBC in comparison to non-irradiated patients (HR = 0.96, 95% CI: 0.58 - 1.59). The joint effects of postlumpectomy RT (HR = 1.37) and strong positive family history for BC (HR = 1.11) on risk of CBC were greater than expected when individual risks were summed (HR = 3.31, 95% CI: 1.96 - 5.60; *P* for departure from additivity = 0.045, Figure 3.3). We hypothesized that RT-induced CBC should occur particularly in the medial part of the contralateral breast, because that part is exposed to the highest radiation dose (Figure 3.1). For a subset of patients, consisting of women treated at the NKI

Table 3.3. Effects of treatment, smoking and family history on CBC risk: multivariate Cox regression analysis in all patients, in patients < 35 years (n= 456), patients from 35 to 45 years (n=1749) and patients from 45 years and older at diagnosis of breast cancer (n=5016)

	Risk of CBC*				
	all patients	age< 35 at BC diagnosis	age 35 - 45 at BC diagnosis	age >= 45 at BC diagnosis	
Risk Factor	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	***P* heterogeneity**
Treatment					
RT vs no RT	1.15 (0.89 – 1.50)	1.78 (0.85 – 3.72)	1.25 (0.83 – 1.88)	1.09 (0.82 – 1.45)	.419
CT vs no CT	0.85 (0.66 – 1.10)	0.67 (0.28 – 1.57)	0.84 (0.57 – 1.26)	0.89 (0.62 – 1.26)	.823
Smoking ever vs. never:					
through the end of follow-up	1.53 (1.15 – 2.04)	2.29 (1.01 – 5.17)	1.36 (0.82 – 2.27)	1.60 (1.10 – 2.32)	.420
ex-smoker	1.10 (0.87 – 1.38)	1.09 (0.48 – 2.47)	1.37 (0.93 – 2.02)	0.99 (0.73 – 1.34)	.502
unknown	1.49 (1.17 – 1.89)	2.39 (1.10 – 5.18)	2.04 (1.34 – 3.11)	1.22 (0.90 – 1.65)	.111
Family history yes vs no/unknown:					
>= 3 relatives with BC	2.39 (1.67 – 3.44)	2.12 (0.50 – 8.97)	2.65 (1.44 – 4.85)	2.29 (1.44 – 3.66)	.894
< 3 relatives with BC	1.94 (1.53 – 2.45)	1.36 (0.56 – 3.29)	1.82 (1.20 – 2.78)	2.07 (1.55 – 2.77)	.627
other types of cancer	1.30 (1.04 – 1.61)	1.23 (0.62 – 2.42)	1.26 (0.86 – 1.87)	1.32 (1.01 – 1.72)	.994

*Adjusted for all variables in the table and for age at diagnosis (5-year categories).

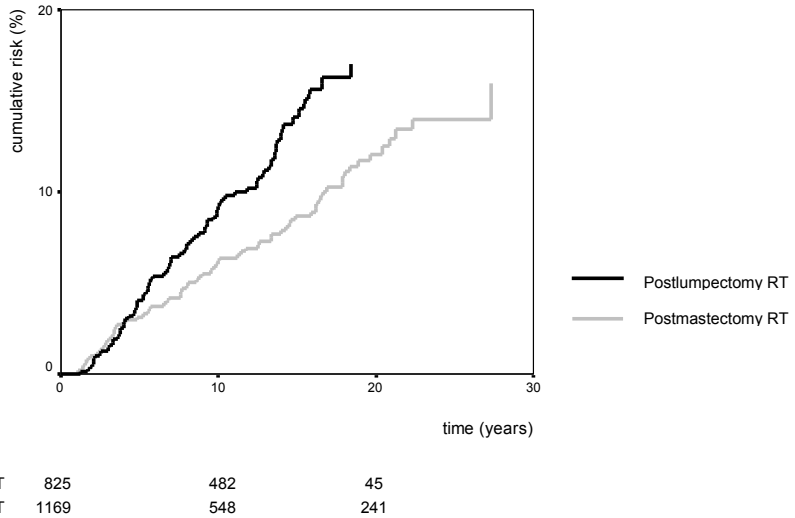


Figure 3.2. Risk of CBC by treatment modality (Cox model), in patients < 45 years at BC diagnosis.
Hazard ratio for postlumpectomy RT vs postmastectomy RT: 1.53 (95% CI,1.11 – 2.09), adjusted for age at BC diagnosis, adjuvant chemotherapy, family history of breast cancer and smoking.

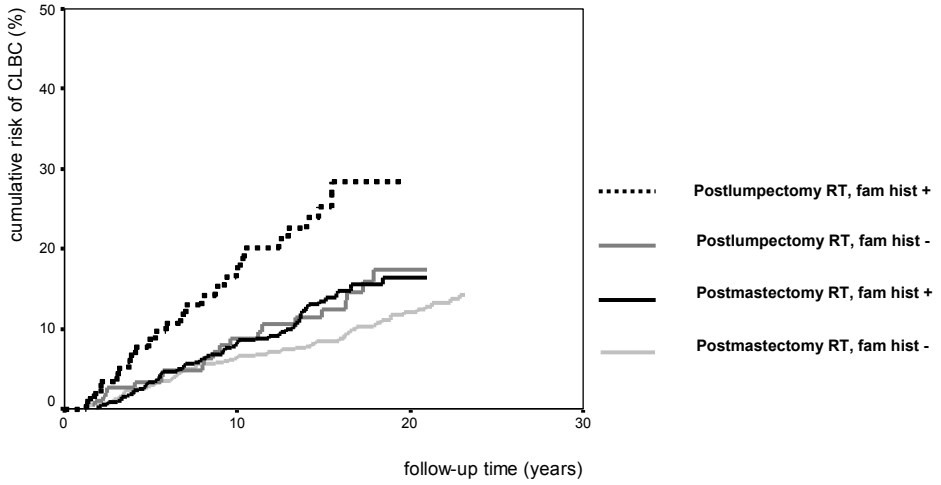


Figure 3.3. Independent and joint effects of RT regimen and family history of breast cancer on CBC risk (Cox model), in patients < 45 years at BC diagnosis

HR* for postlumpectomy RT and positive** family history, 3.31 (95% CI: 1.96 – 5.60); P for departure from additivity, 0.045.

HR* for postlumpectomy RT and negative family history, 1.37 (95% CI: 1.00 – 1.87);

HR* for postmastectomy RT and positive family history, 1.11 (95% CI: 0.49 – 2.55);

HR* for postmastectomy RT and negative family history, 1.00 (reference).

* adjusted for age at BC diagnosis, adjuvant chemotherapy and smoking.

** positive family history: 3 or more relatives diagnosed with breast cancer.

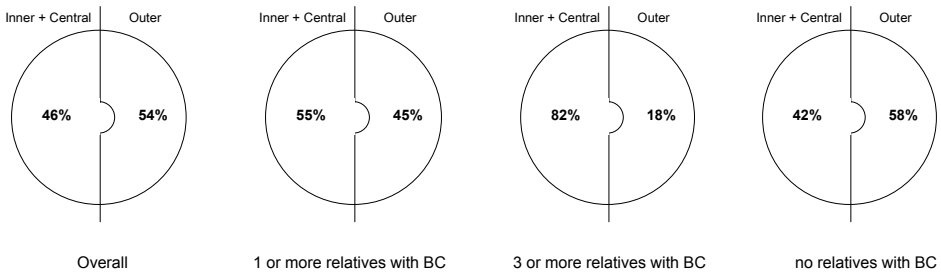


Figure 3.4. Distribution of localization of contralateral breast cancer by family history of breast cancer, in patients irradiated < age 45 years for breast cancer at the NKI (n = 943).

before age 45 years (*n* = 1044), we collected data on the localization of the CBC. Overall, the proportions of CBC developing in medial and lateral quadrants were 46% and 54%, respectively (Figure 3.4). However, when we stratified by family history of BC, a medial location of CBC occurred in 55% of patients with 1 or more relatives with BC, and even in 82% of patients with 3 or more relatives with BC, against 42% medially located CBCs in patients with no family history of BC (*P* for difference = 0.01). Using a Cox model with medially located CBC as outcome in the same subset of patients rendered HRs of 1.23, 2.72 and 5.26 for average radiation doses to the medial part of the contralateral breast of 0-3.6 Gy, 3.6–6.6 Gy and >=6.6 Gy, respectively, in comparison with no RT (Table 3.4a). The dose-response relationship for

Table 3.4a. Effect of radiation dose on risk of medially located CBC;
multivariate Cox regression analysis in patients treated at the NKI < 45 years (n= 1044)

Radiation dose to medial part of contralateral breast	Risk of medial CBC*
Gy	HR (95% CI)
0	1.0 (ref.)
0 – 3.6	1.23 (0.34 – 4.48)
3.6 – 6.6	2.72 (0.75 – 9.79)
>= 6.6	5.26 (1.44 – 19.3)
Linear ERR per Gy**	0.37 (0.04 – 1.78), p=0.0129 (trend)

Abbreviations: CBC, contralateral breast cancer; HR, hazard ratio; ERR, excess relative risk.
* Adjusted for age (continuous), adjuvant chemotherapy
**Based on model RR=1+beta*dose where beta=ERR

Table 3.4b. Effect of radiation dose on risk of any CBC;
multivariate Cox regression analysis in patients treated at the NKI < 45 years (n= 1044)

Average radiation dose to contralateral breast	Risk of any CBC*
Gy	HR (95% CI)
0	1.0 (ref.)
0 – 2.2	0.95 (0.49 – 1.84)
2.2 – 4.1	1.67 (0.85 – 3.27)
>= 4.1	2.15 (1.04 – 4.43)
Linear ERR per Gy**	0.21 (0.01 – 0.61), p=0.0318 (trend)

Abbreviations: CBC, contralateral breast cancer; HR, hazard ratio; ERR, excess relative risk.
* Adjusted for age (continuous), adjuvant chemotherapy
**Based on model RR=1+beta*dose where beta=ERR

risk of any CBC by average radiation dose to the contralateral breast showed a linear excess relative risk (ERR) of 0.21 per Gy increase, while the relationship was much stronger for risk of medially located CBC by average radiation dose to the medial part of the contralateral breast (linear ERR/Gy = 0.37; *P* for trend = 0.01, Table 3.4a,b). Also, a time-dependent Cox model showed a clear increase of radiotherapy-associated risk of medially located CBC with longer follow-up (HR = 1.6 during the first 5 years of follow-up, and HRs of 2.6 and 3.2 in the 5- to 15-year and >15 year follow-up intervals, respectively; *P* for trend = 0.004).

Adjuvant CT was associated with a nonsignificantly decreased risk of CBC (HR = 0.83), further decreasing with younger age at first treatment (HRs for patients <45 and <35 years at BC diagnosis, 0.76 and 0.61, respectively; Table 3.5). When we included all contralateral breast tumors, as frequently done in other studies, rather than only those without distant metastases up to 6 months after CBC diagnosis, adjuvant CT appeared to exert a larger and statistically significant protective effect on risk of CBC (HR = 0.76), which was even stronger in patients < 45 years at first treatment (HR = 0.69, Table 3.5). Time-dependent analysis showed that the CT-associated decrease in risk disappeared after more than 5 years of follow-up (Table 3.5).

Table 3.5. Effect of chemotherapy on risk of CBC: multivariate Cox regression analysis in all patients (n= 7221), and in patients < 45 years at diagnosis of breast cancer (n = 2205)

	Risk of CBC*			
CT vs no CT	**all patients**		**patients < 45 at BC diagnosis**	
	Strict definition†	**Broader definition#**	**Strict definition†**	**Broader definition#**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Overall:	0.83 (0.65 – 1.08)	0.76 (0.61 – 0.95)	0.76 (0.53 – 1.10)	0.69 (0.50 – 0.95)
Time-dependent model:				
first 5 years of follow- up	0.81 (0.52 – 1.26)	0.60 (0.42 – 0.86)	0.66 (0.35 – 1.28)	0.48 (0.28 – 0.82)
follow-up of 5 years and more	0.90 (0.66 – 1.22)	0.90 (0.68 – 1.20)	0.87 (0.56 – 1.35)	0.89 (0.60 – 1.34)

Abbreviations: CBC, contralateral breast cancer; CT, chemotherapy; HR, hazard ratio.

*Adjusted for age

† Strict definition of CBC as used in Tables 3.2, 3.3 and 3.4.

Broader definition of CBC applied to our study population: invasive cancer in the contralateral breast diagnosed at least 3 months after the first BC, regardless of the presence of metastatic disease at the date of diagnosis of CBC, thus rendering 175 more cases of CBC.

For example, in patients treated before age 45, the HR associated with CT was 0.48 in the first 5 years of follow-up (using the broader definition of CBC), while no risk decrease was noted 5 or more years after CT (HR = 0.89; 95% CI: 0.60 - 1.34).

Discussion

In this large and long-term follow-up study of BC patients treated between 1970 and 1986, RT did not significantly increase the risk of CBC overall. However, the association with RT became stronger with younger age at BC diagnosis. Furthermore, irradiated women who received postlumpectomy RT before age 45 experienced greater risk of CBC compared with patients of the same age who had received postmastectomy RT. The dose-response relationship between radiation and risk of CBC became stronger when relating the radiation dose received by the medial portion of the breast to the development of CBC in the same area, supporting a role for RT to induce malignancy in the contralateral breast. To our knowledge our study is the first one examining the effects of combined exposure to RT and family history of breast cancer. Remarkably, we found for the subset of patients younger than 45, that the joint effects of postlumpectomy RT and a positive family history of BC on CBC risk were greater than expected when individual risks were summed.

We could only observe an association between adjuvant CT and decreased risk of CBC in the first 5 years of follow-up; our data suggest that CT primarily affects CBC risk by eradicating pre-existing tumor cells in the contralateral breast. Finally, continued smoking was also associated with an increased risk of CBC.

In general it has been demonstrated that radiotherapy may reduce both the risk of local recurrence and death from BC.[13] Data regarding the RT-associated risk of CBC are inconsis-

tent.[5,6,9,10,12,13,33] Most studies did not show an increased risk of CBC after radiotherapy. However, in many studies the number of patients and follow-up time may have been insufficient to fully assess the risk of CBC. In a large case-control study based on the Connecticut Tumor Registry, Boice et al.[9] observed significantly elevated risks for women who underwent irradiation before age 45 (relative risk (RR), 1.59). However, patients in this study were treated between 1935 and 1982, with RT regimens considered obsolete nowadays, while postlumpectomy RT was not yet administered. More recently Gao et al., using the SEER database (1973-1996), demonstrated an overall effect of RT on CBC risk (RR, 1.14) in 5-year survivors.[12] Similar results were published in the latest meta-analyses of the EBCTCG[13] on effects of RT (1976-1991) on local recurrence and 15-year survival (RR, 1.18). Unfortunately, these two studies did not examine CBC risk according to the type of RT regimen. Obedian et al. compared risk of second malignancies between patients treated by postlumpectomy RT and by mastectomy without RT.[10] Patients aged 45 years or younger who underwent postlumpectomy RT had a nonsignificantly higher 15-year risk of CBC than did patients who underwent surgery only (10% vs 7%).

We found increased CBC risk specifically for breast irradiation using tangentials. In our study patients who received postlumpectomy RT routinely underwent treatment using both medial and lateral wedges. The use of a medial wedge has been shown to increase the amount of scatter radiation to the contralateral breast.[34,35] Several studies have shown that the contralateral breast generally receives a radiation scatter dose of 0.5 – 4 Gy, depending on the radiation technique used.[36-38] These doses are well within the range known to induce breast cancer, particularly when received at young ages.[18,39-41] Based on our dosimetry model doses up to 4.6 Gy (when using ^{60}Co) were estimated from tangential breast RT plus boost. IMC RT using ^{60}Co rendered doses in the same range in case of use of ^{60}Co; with the use of electrons, however, the dose dropped dramatically. Since breast conserving therapy implied at least tangential breast fields, postlumpectomy RT probably resulted in a much higher dose to the contralateral breast than postmastectomy RT. For example, in case of irradiation to the breast plus IMC, the typical dose to the inner quadrants of the contralateral breast was between 2.1 and 7.4 Gy, and to the outer quadrants between 0.8 and 3.0 Gy. By contrast, using postmastectomy RT with direct electron field plus IMC field, the inner and outer quadrants received doses ranging from 0.6 - 3.6 Gy and 0.1 - 1.3 Gy, respectively. These differences in RT exposure are likely to explain the differences in risk of CBC as found between patients treated with postlumpectomy RT and postmastectomy RT. This is also illustrated by results from the dose-response analysis in Table 3.4; the RT-associated risks for the consecutive categories of estimated radiation dose received on the medial part of the contralateral breast (below or beyond 3.6 Gy) corresponded well with the distinction made between postlumpectomy and postmastectomy RT. Our finding of predominantly medially located CBCs in irradiated patients with strong family history of BC confirms our hypothesis that specifically in high-risk women RT may induce the development of a second breast cancer.

Over the last decades radiation techniques for treatment of BC patients have gradually improved. The introduction of intensity modulated radiotherapy (IMRT) will not only lead to a more homogeneous dose distribution in the affected breast, but also to a lower dose to the contralateral breast because when applying IMRT the use of a medial wedge can be avoided and the number of monitor units is usually lower with IMRT as compared to convential RT using wedged tangential fields.[35,42] Furthermore the indication for IMC radiation is stricter than before.

Studies of BC among atomic bomb survivors showed that among women younger than 20 years of age at the time of the explosions, the excess RR per unit dose equivalent was greatest among women with early-onset breast cancer, defined as breast cancer diagnosed before age 35.[18] The authors suggested that a subgroup of the population may be genetically susceptible to radiation-induced breast cancer. Whether the risk of radiation-induced breast cancer is higher among women with a genetic predisposition to breast cancer, such as due to inherited mutations in the BRCA1, BRCA2 or p53 genes, has been examined in very few studies. Recently, Andrieu et al. reported an association between exposure to chest X-rays and increased risk of BC in BRCA carriers, particularly when exposed at a young age.[43] Furthermore, in a related case-only study we found that carriers of germline mutations in the DNA-damage repair pathway genes BRCA1, BRCA2, CHEK2 and ATM have an increased risk of developing radiation-associated CBC compared with non-carriers.[44] In view of the increased risk of CBC in BRCA1 and BRCA2 mutation carriers and the evidence that both BRCA1 and BRCA2 are involved in repair of radiation-induced DNA damage, the rationale for breast-conserving therapy in mutation carriers has been questioned. Sofar, few studies addressed this issue, however. Metcalfe et al., who studied risk factors for CBC in BRCA 1/2 carriers, found no indication for RT to play a role in the increased risk of CBC.[45] However, the analysis was not restricted to the subset of young women and information on specific RT regimens was not available. We found that the joint effects of postlumpectomy RT and family history of BC on CBC risk were greater than expected when individual risks were summed, suggesting increased susceptibility to radiation-induced breast cancer in women carrying mutations in breast cancer susceptibility genes.

As for the effect of smoking on risk of CBC, reports are contradictory, probably as a result of opposite mechanisms. The overall carcinogenic effect of smoking may be counteracted by smoking-related earlier menopause, which may lead to a decreased risk of CBC. Thus, the risk increase would be expected particularly in younger, premenopausal patients. In our data risk of CBC associated with smoking appeared to increase with age < 35 years at BC diagnosis (HR = 2.21; 95% CI: 0.91 - 5.38). However, too many patients had missing information on smoking to draw any further conclusions. Furthermore, smoking may well be confounded by alcohol use, a variable we were not able to control for.

Our data suggest a risk reduction from adjuvant CT, but this result was not statistically significant and the effect size was much smaller than in other studies.[3,5,6] This may be related to our

strict definition of CBC and our long-term follow-up. When we changed our definition of CBC by including CBCs diagnosed in the presence of distant metastases, it appeared that the protective effect of CT became much stronger (50% risk reduction). Likely, a large part of the risk reduction after CT is due to eradication of occult microscopic disease in the opposite breast, which does not seem to be modified by age. A smaller part of the reduction of CBC risk may also be due to CT-induced premature ovarian failure, a phenomenon expected exclusively in younger women. Interestingly, the risk reduction disappeared after more than 5 years of follow-up, as was reported by Cook et al.[6] This argues against an important contribution of CT-induced premature menopause, as early menopause is known to exert a long-lasting effect on BC risk.

When interpreting our results, the strengths and limitations of our study should be considered. Unlike most other studies, we collected detailed information on all primary and follow-up treatments, including RT regimens and potential risk factors (smoking, family history). Follow-up was near complete and very long, with almost 20% of patients followed for more than 20 years. Clearly, length of follow-up will influence the median interval up to the event of interest. In our study the median period to the development of a CBC was 7.7 years, emphasizing the importance of long-term surveillance of BC patients.

An ever recurring problem in studies of CBC risk is the difficulty to distinguish CBC from metastases of the first primary BC. Most larger studies on CBC risk have employed a broad definition for CBC, by including all women with contralateral tumors occurring at any time. However, unlike other studies, we had information on the dates of distant metastases. Therefore, we could use a stricter definition, excluding CBCs with distant metastases up to 6 months after the diagnosis of CBC. This should have improved the ascertainment of "true" CBCs. Some recent studies used molecular-genetic techniques to differentiate between metastasis and second primary BC and showed that most localized CBCs were indeed distinct entities.[46]

A limitation of our study is that germ-line mutation test results for BRCA1, BRCA2 or other predisposing genes were not available at the time of diagnosis for the patients in this study. We used family history as a surrogate measure and identified a subgroup of women with a positive family history of BC at significantly increased risk for CBC.

In conclusion, our data show that modern RT increases the risk of CBC in women irradiated before age 45, with a clear dose-response relationship. Furthermore, patients with a strong family history of BC are more susceptible to radiation-induced BC than patients without affected relatives. Clearly the question whether RT following BCT is appropriate for young patients who carry predisposing mutations, is not yet settled. Future studies are warranted to further evaluate the increased risk of CBC from tangential breast fields overall, and in BRCA1/2 carriers in particular.

Acknowledgment

We thank M.A. Kuenen, V.B. Hartog and A.W. van den Belt–Dusebout for assistance in data collection, T. van de Velde (cancer registry of the Netherlands Cancer Institute) for supplying us with detailed information on RT regimens, and W.J. Klokman for statistical advice on the person-year-analysis program.

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4 Long-term risk of cardiovascular disease in 10-year survivors of breast cancer

Maartje J. Hooning, Akke Botma, Berthe M.P. Aleman, Margreet H.A. Baaijens, Harry Bartelink, Jan G.M. Klijn, Carolyn W. Taylor, Flora E. van Leeuwen

J Natl Cancer Inst 2007; 99: 365-75

Abstract

Background

Radiotherapy for breast cancer as delivered in the 1970s has been associated with increased risk of cardiovascular disease, but recent studies of associations with modern regimens have been inconclusive. Few data on long-term cardiovascular disease risk according to specific radiation fields are available, and interaction with known cardiovascular risk factors has not been examined.

Methods

We studied treatment-specific incidence of cardiovascular disease in 4414 10-year survivors of breast cancer who were treated from 1970 through 1986. Risk of cardiovascular disease in these patients was compared with general population rates and evaluated in Cox proportional hazards regression models. All statistical tests were two-sided.

Results

After a median follow-up of 18 years, 942 cardiovascular events were observed (standardized incidence ratio = 1.30; 95% confidence interval [CI]: 1.22 - 1.38; corresponding to 62.9 excess cases per 10,000 patient-years). Breast irradiation only was not associated with increased risk of cardiovascular disease. However, radiotherapy to either the left or right side of the internal mammary chain was associated with increased cardiovascular disease risk for the treatment period 1970–1979 (for myocardial infarction, hazard ratio [HR] = 2.55; 95% CI: 1.55 - 4.19; $P<.001$; for congestive heart failure, HR = 1.72; 95% CI: 1.22 - 2.41; $P=.002$) compared with no radiotherapy. Among patients who received internal mammary chain radiotherapy after 1979, risk of myocardial infarction declined over time toward unity, whereas the risks of congestive heart failure (HR = 2.66; 95% CI: 1.27 - 5.61; $P=.01$) and valvular dysfunction (HR = 3.17; 95% CI: 1.90 - 5.29; $P<.001$) remained increased. Patients who underwent radiotherapy plus adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only (HR = 1.85; 95% CI: 1.25 - 2.73; $P=.002$). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (HR = 3.04; 95% CI: 2.03 - 4.55; P for departure from additivity = .039).

Conclusions

Radiotherapy as administered from the 1980s onward is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease.

Introduction

During the past 30 years, survival of breast cancer patients has improved substantially due to earlier diagnosis, introduction of combination chemotherapy and hormonal treatment, and refinement of radiation techniques.[1] However, several studies have demonstrated that breast cancer patients who were treated with adjuvant radiation have an increased risk of mortality from ischemic heart disease.[2-5] Most of these studies are of patients who were treated with radiotherapy during the 1960s and 1970s, when radiation therapy used techniques that are now considered suboptimal. Studies of more modern regimens administered during the 1980s show inconclusive results for both postmastectomy radiotherapy and breast-conserving therapy.[6-11] Few long-term data are available, but previous studies[2,3,12] have shown that radiotherapy-related cardiac risk may become manifest only after 10 or more years since first treatment. To date, there have been no reports of the associations of specific radiotherapy fields in relation to cardiac disease, and differences in fields might partly explain the different results between studies. Furthermore, only cardiac mortality, not morbidity, has been investigated in most studies, although cardiac morbidity has a serious impact on the life expectancy and quality of life of long-term survivors.

We report here on the incidence of cardiac disease in the Dutch Late Effects Breast Cancer cohort of 4414 10-year survivors who were treated between 1970 and 1986. Unique features of this study include long-term and near-complete follow-up, the assessment of cardiac risk according to radiation field, and the incorporation of cardiac risk factors into analyses.

Patients and methods

Data collection procedures

The Late Effects Breast Cancer Cohort consists of 7425 1-year female breast cancer survivors, younger than age 71 years at diagnosis, treated for stages I, II, and IIIA from 1970 through 1986 at the Netherlands Cancer Institute (NKI) or the Erasmus MC, Daniel den Hoed Cancer Center (DDHK). A detailed description of data collection procedures has been published previously.[12] In brief, all patients were identified through the hospital-based cancer registries of the two centers. From the registries and the patient records, we collected date of breast cancer diagnosis, tumor histology, axillary lymph node involvement, dates and treatment modalities of primary breast cancer and of recurrent disease (type of surgery, radiation fields, chemotherapy, hormonal treatment), history of cardiac disease before diagnosis of breast cancer, dates of diagnoses of cardiac events, cardiovascular risk factors, date of most recent medical information or date of death, and primary cause of death according to International Classification of Diseases, 9th Revision.[13] Risk factors (smoking, hypertension, diabetes mellitus, and hypercholesterolemia) were recorded both at the date of diagnosis of breast cancer

and at the end of follow-up. Patients were considered as smokers if they were smokers at the end of follow-up or had stopped smoking less than 1 year before the end of follow-up. Patients were scored positive for hypertension if they had received treatment for high blood pressure or had a diastolic blood pressure that exceeded the limit of 95 mm Hg on two occasions. Patients who had been treated for diabetes mellitus or hypercholesterolemia were scored as positive for these conditions.

We restricted this study to all 10-year survivors (n = 4414) because we have shown in a previous report on mortality in the Late Effects Breast Cancer Cohort[12] that the increase in cardiac risk associated with radiotherapy does not emerge until 10 years after treatment. Data regarding specific cardiac diagnoses and risk factors for all patients were updated through January 1, 2000, or later by questionnaire to the patients' general practitioners. In The Netherlands, nearly all residents have a general practitioner who receives all medical correspondence from attending physicians. Forty-six patients were excluded from the 10-year survivors' cohort because their patient records did not contain information after 10 years since diagnosis of breast cancer and no additional information could be obtained from their general practitioners. For the remaining 4368 patients, we collected cardiac data for 83% of the patients from both the patient record and the general practitioner and for the other 17% from the patient records only. Complete follow-up information through at least January 1, 2000, was eventually available for 4259 (96%) of all 10-year survivors. For patients who died from an acute cardiac event and had no prior evidence of cardiac disease, the date of death was recorded as date of diagnosis of the cardiac event.

Treatment

During the early 1970s, standard treatment for stages I, II, and IIIA breast cancers consisted of modified or radical mastectomy, with or without radiotherapy. In 1975, adjuvant systemic treatment was introduced for lymph node–positive patients; combination chemotherapy for premenopausal patients, and, gradually, from 1980 onward, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of CMF (cyclophosphamide, methotrexate and fluorouracil) during the entire study period; until 1980, 12 cycles were administered, afterwards only six. In 1980, both hospitals introduced breast-conserving therapy that consisted of wide local excision and axillary lymph node dissection, followed by whole-breast irradiation.[14]

The radiotherapy regimen depended on type of surgery and stage of disease, with some differences between the two cancer centers. In the NKI, irradiation of the ipsilateral internal mammary chain field was common during the entire study period (1970–1986) for patients who had centrally or medially located tumors and/or axillary lymph node metastases. Patients who had extensive axillary nodal metastases also had irradiation to the axilla and supraclavicular nodes. Chest wall irradiation was given to patients with incomplete resection or extensive primary tumors. After breast-conserving therapy, the breast was always irradi-

ated postoperatively. In the DDHK, 60% of patients with centrally or medially located tumors and/or axillary lymph node metastases were treated with radiation to the internal mammary chain field. Indications for irradiation of the axilla, supraclavicular nodes, chest wall, or breast were comparable to the indications used in the NKI. The dose to the internal mammary chain field varied from 40 Gy in 15 fractions to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and electrons; the chest wall received doses between 35 Gy and 45 Gy in 15 to 20 fractions, using electrons. Breast irradiation consisted of a dose of 50 Gy in 25 fractions using two tangential photon beams (4–8 MV or cobalt-60), followed by a boost of 15–25 Gy to the tumor bed, using an iridium implant.

Dosimetry for estimation of radiation dose to the heart

Radiation equipment and techniques changed considerably over the years. Although the regions irradiated were known for every patient, the individual cardiac radiation doses could not be calculated because we had no information on the specific regimens used. However, based on the distribution of these different techniques for the years 1970-1986 in a random sample of 160 patients, we could roughly estimate the mean cardiac doses received by patients in our study who were irradiated at specific regions.

Heart dose estimations were performed by one of the authors (C.W. Taylor) in Oxford, UK, at the Clinical Trial Service Unit of Oxford University. For each specific radiotherapy regimen, we determined the technique, typical dose, the beam energy involved, and field borders. The estimated dose of radiation to the heart was based on virtual simulation[15,16] and computed tomography planning (Helax TMS version 6.1B, Nucletron Ltd, Veenendaal, The Netherlands). The computed tomography planning scans were of patients set up with a T-bar arm rest, similar to that of immobilization techniques used in breast treatments in previous decades. A series of approximately 40 scans were reviewed, and one patient of average weight and build was selected as a representative patient for whom all dose estimations were performed. The three-dimensional patient surface and lung contours were defined by automated density gradient tracking. The heart and coronary arteries were contoured by a radiation oncologist and reviewed by a radiologist. Virtual simulation software was used to identify relevant skin and bony landmarks. For each radiotherapy technique, beam arrangements were set up and exported to a computed tomography planning computer. Dose plans were evaluated, dose volume histograms were generated, and mean heart dose was calculated.

Statistical analysis

We compared the incidence of cardiovascular diseases in the study population with the incidence in the Dutch female population, taking into account the person-years of observation in the cohort (by age, calendar period, and follow-up interval). Incidence data of the Continuous Morbidity Registration Nijmegen (CMRN),[17] which are derived from several general practitioners' practices from representative regions in The Netherlands, were used as reference rates.

This registry has collected data on the incidence of myocardial infarction, angina pectoris, and congestive heart failure for the period 1972–2000, allowing for multiple separate diagnoses per person but recording only the first of a specific diagnosis per person.[18] Comparison of recent incidence rates of myocardial infarction and angina pectoris from the CMRN with those of several new registries in The Netherlands, including only short-term incidence rates, showed similar rates for CMRN and for the other registries combined, indicating that the CMRN is representative of The Netherlands.[19]

To assess treatment effects on risk of cardiovascular disease, we distinguished five mutually exclusive treatment categories that were defined by all treatments received up to 1 year before end of follow-up: 1) surgery only, 2) radiotherapy with or without surgery, 3) radiotherapy and chemotherapy with or without surgery, 4) radiotherapy and hormone therapy with or without surgery, and 5) radiotherapy, chemotherapy, and hormone therapy with or without surgery. Treatments given in the last year of follow-up were excluded from the analysis because the period following salvage treatment was too short for long-term effects of treatment to emerge. Time at risk began 10 years after the start of first treatment and ended at the date of diagnosis of a specific cardiac event, date of death, or date of most recent medical information, whichever came first. In the analysis by laterality, time at risk would end at date of a contralateral breast cancer, but only if the patient had received radiotherapy to the contralateral side. Observed numbers of a cardiovascular diagnosis were based on all first events of a specific cardiovascular diagnosis occurring after 10 years of follow-up time because the expected numbers of events were recorded correspondingly; patients who were diagnosed with a specific cardiovascular event before breast cancer diagnosis or within 10 years since first treatment were excluded from the analysis. The standardized incidence ratios (SIRs) of the observed and expected numbers of myocardial infarction, angina pectoris, and congestive heart failure in the study population were determined, and the confidence limits of the standardized incidence ratios were calculated using exact Poisson probabilities of observed numbers.[20] *P* values for tests for trend were two-sided and were calculated using chi-square test statistics. $P<.05$ was considered statistically significant. Absolute excess risk was calculated by subtracting the expected number of cardiovascular disease events in our cohort from the number observed and dividing by person-years at risk (expressed per 10,000 person-years).

The Cox proportional hazards model[21] was used to quantify the effects of different treatments on cardiovascular disease risk taking into account several covariates (age at treatment, cardiovascular risk factors). The assumptions of proportionality were verified by comparing log-log survival curves. To evaluate the independent effects of primary treatment, we did a separate analysis in which time at risk ended at date of treatment for recurrent disease. Cox models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL).

Biologic interaction was evaluated as departure from additivity of the effect of two risk factors, for which the interaction risk is the risk that cannot be explained by the joint exposure

to both risk factors, as expressed in the following formula[22]: $R_{INT} = R_{A+B} - (R_A + R_B - R_U)$, for which A and B are risk factors; R_{INT} is interaction risk, and R_U is background risk. We performed statistical analysis to determine whether the joint effect was different from that of a single factor. For this test, we used EPICURE software.[23] The test was based on the null hypothesis $\gamma = 0$ in $R_{A+B} = (R_A + R_B - R_U + \gamma)$, i.e., allowing for an additive departure (γ) from an additive joint effect. The test was a two-sided likelihood ratio test.

Results

Patient characteristics

Approximately half of all patients were treated in the period of 1970–1980 and the other half between 1981 and 1986 (Table 4.1). Overall, median age at breast cancer diagnosis was 49 years. Median follow-up time was 17.7 years, and 31% of the patients were followed for more than 20 years. More than half (54%) of the study population was treated with surgery plus radiotherapy; 12% with surgery, radiotherapy, and chemotherapy; and 12% with surgery only. More than half (58%) of the patients received internal mammary chain irradiation, 30% received breast irradiation, and 20% received chest wall irradiation.

Information on smoking habits was available for 88% of the patients: 49% had never smoked, 32% smoked at the time of breast cancer diagnosis, and 10% still smoked at the end of follow-up (Table 4.2). Hypertension was reported in 26% of the patients during any time from breast cancer diagnosis until the end of follow-up, diabetes mellitus in 9%, and hypercholesterolemia in 10%.

Risk of cardiovascular disease by age and follow-up interval

Incidence of cardiovascular disease was recorded (Table 4.3). After a median follow-up of 18 years, 942 cardiovascular events were observed (SIR = 1.30; 95% confidence interval [CI]: 1.22 - 1.38; 62.9 excess cases per 10,000 patient-years). Heart failure was the most frequently observed cardiovascular event (n = 382 out of 942 diagnoses). The study population experienced moderately but statistically significantly increased risks of myocardial infarction (SIR = 1.23), angina pectoris (SIR = 1.30), and congestive heart failure (SIR = 1.35) compared with the general female population, with absolute excess risks of 13.5, 20.6, and 28.7 per 10,000 patient-years, respectively (Table 4.3). The standardized incidence ratio for angina pectoris increased with follow-up duration (Table 4.4), from 1.09 for 10–14 years since first treatment to 1.70 at 20 years and later, corresponding to absolute excess risks of 5.5 and 59.9 per 10,000 patient-years, respectively. For myocardial infarction and congestive heart failure, there was no trend over time. The risk of congestive heart failure was highest among patients who were youngest at first treatment (for the age group of 35–44 years, SIR = 3.64; for those younger than 35 years, SIR = 6.54). The same pattern was seen with attained age (for developing con-

Table 4.1. Characteristics of 10-year survivors in the Dutch Late Effects Breast Cancer Study

	Characteristic	No. of patients	%
	No. of patients	4368	100
Hospital	NKI	2045	46.8
	DDHK	2323	53.2
Age at breast cancer diagnosis, y	< 45	1379	31.6
	45–54	1681	38.5
	≥ 55	1308	29.9
Year of first treatment of breast cancer	1970–75	1075	24.6
	1976–80	1059	24.2
	1981–86	2234	51.1
Axillary node involvement at diagnosis	Node negative	2557	58.5
	Axillary node positive, subclavicular node negative	1544	35.3
	Subclavian node positive	164	3.8
	Unknown	103	2.4
Laterality	Left	2229	51.0
	Right	2097	48.0
	Bilateral	42	1.0
Treatment category, primary + follow-up treatment	Surgery only	516	11.8
	RT (+ surgery)	2362	54.1
	RT + CT (+ surgery)	529	12.1
	RT + HT (+ surgery)	438	10.0
	RT + CT + HT (+ surgery)	448	10.3
	Other/unknown	75	1.7
Radiation fields, primary + follow-up treatment†	IMC	2538	58.1
	Chest wall	880	20.1
	Breast	1319	30.2
	McWhirter (supraclavicular + axillary field)	1017	23.3
	Supraclavicular	44	1.0
	Axilla	339	7.8
Radiation fields, primary + follow-up treatment‡	IMC, no chest wall or breast	1453	33.3
	Chest wall, no IMC	388	8.9
	Breast, no IMC	688	15.8
	IMC + chest wall	477	10.9
	IMC + breast	608	13.9
	Other fields; but no IMC, chest wall or breast	85	1.9
	Unknown	60	1.4
Follow-up time, y	10–14	1081	24.7
	15–19	1917	43.9
	≥ 20	1370	31.4

Abbreviations: NKI, Netherlands Cancer Institute; DDHK, Erasmus MC, Daniel den Hoed Cancer Center; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy; IMC, internal mammary chain; y, years.

†Allowing more than one field per patient.

‡Mutually exclusive treatment groups.

Table 4.2. Risk factors for cardiovascular disease in 10-year survivors of the Dutch Late Effects Breast Cancer Study

	Characteristic	No. of patients	%
Smoking	Never	2136	48.9
	Unknown at breast cancer diagnosis, but not at end of follow-up	334	7.6
	Smoking at breast cancer diagnosis, but not anymore at end of follow-up	413	9.5
	Smoking at breast cancer diagnosis, unknown at end of follow-up	551	12.6
	Smoking through the end of follow-up	426	9.8
	Unknown	508	11.6
Hypertension	No	3039	69.5
	Diagnosed before breast cancer diagnosis	444	10.2
	Developed during follow-up	716	16.4
	Unknown	169	3.9
Diabetes mellitus	No	3826	87.6
	Yes	383	8.8
	Unknown	159	3.6
Hypercholesterolemia	No	3739	85.6
	Yes	441	10.1
	Unknown	188	4.3
History* of cardiovascular disease	No/ Unknown	4213	96.4
	Ischaemic heart disease	77	1.8
	Congestive heart failure	12	0.3
	Valvular disorders	26	0.6
	Dysrhytmias	27	0.6
	Other	13	0.3

*Before breast cancer diagnosis.

gestive heart failure before age 55, SIR = 4.25), with declining risks as attained age increased (P_{trend} <.001). Analyses by laterality showed slightly but statistically nonsignificantly higher standardized incidence ratios of cardiovascular disease for patients with left-sided breast cancer than for those with right-sided breast cancer (Table 4.4). In total, 167 patients died from cardiovascular disease, mostly from acute myocardial infarction or congestive heart failure.

Risk of cardiovascular disease in relation to treatment

Risks of myocardial infarction, angina pectoris, and congestive heart failure were statistically significantly increased in irradiated patients compared with the rates in general female population (SIR = 1.33; 95% CI: 1.14 - 1.55; SIR = 1.42; 95% CI: 1.23 - 1.63; and SIR = 1.23; 95% CI: 1.07 - 1.40, respectively; Table 4.4). Conversely, patients who were treated with surgery only experienced a lower risk of myocardial infarction than the general population (SIR = 0.68; 95% CI: 0.43 - 1.03). With regard to congestive heart failure, the risk was strongly associated with chemotherapy (for radiotherapy plus chemotherapy treatment vs radiotherapy only, SIR = 3.48 versus SIR = 1.23; relative risk [RR] = 2.84; 95% CI: 1.96 - 4.00).

Table 4.3. Standardized incidence ratios for cardiovascular diseases in 10-year survivors of breast cancer

Diagnosis	ICD-9 code	Obs	Exp	SIR	(95% CI)	AER*
Ischemic heart disease	410–414					
Acute myocardial infarction	410	254	206.6	1.23	(1.08 to 1.39)	13.5
Angina pectoris	411–414	306	235.9	1.30	(1.16 to 1.45)	20.6
Other heart diseases	420–429					
Pericarditis	420, 423	22	—	—	—	—
Valvular dysfunction	424	186	—	—	—	—
Cardiomyopathy	425	56	—	—	—	—
Dysrhytmias	427	333	—	—	—	—
Congestive heart failure	428	382	282.6	1.35	(1.22 to 1.49)	28.7
Cardiovascular disease†	410–414, 428	942	725.1	1.30	(1.22 to 1.38)	62.9

Abbreviations: ICD-9, International Classification of Diseases, 9th revision; Obs, observed number of events; Exp, expected number of events; SIR, standardized incidence ratio; CI, confidence interval; —, no reference rates available for pericarditis, valvular dysfunction, cardiomyopathy, or dysrhythmias. *AER, Absolute excess risk per 10,000 patients per year; †Combined group, allowing more than one event per person: both myocardial infarction and angina pectoris were reported in 70 patients, both myocardial infarction and congestive heart failure were reported in 40 patients, both angina pectoris and congestive heart failure were reported in 66 patients, myocardial infarction, angina pectoris and congestive heart failure were reported in 34 patients.

Comparisons within the cohort

Overall, radiotherapy (compared with surgery only) was associated with an increased risk of cardiovascular disease (hazard ratio [HR] = 1.41; 95% CI: 1.14 - 1.74). To determine whether changes in treatment during the study period influenced risk of cardiovascular disease, we

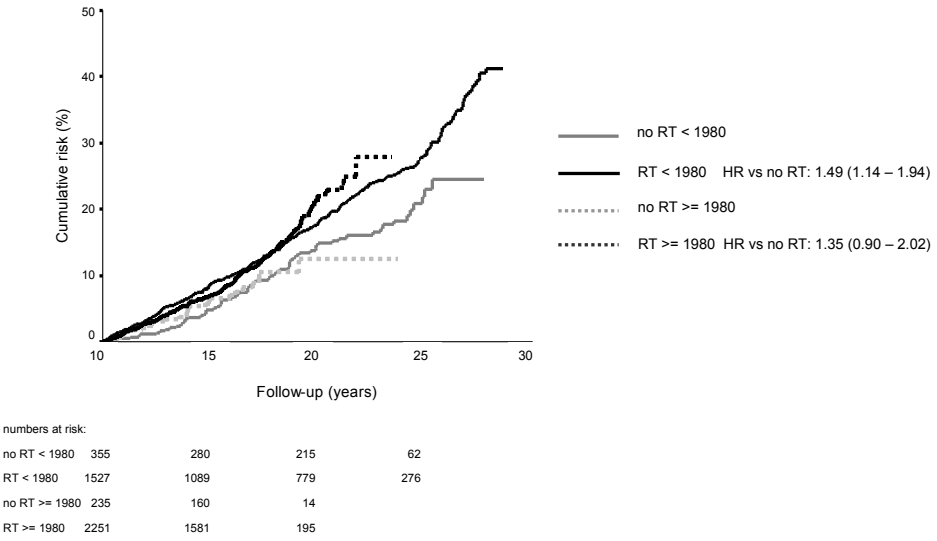


Figure 4.1. Risk of cardiovascular disease by RT and treatment period (Cox model), adjusted for age. RT= radiotherapy; HR= hazard ratio.

Table 4.4. Risks of myocardial infarction, angina pectoris, and congestive heart failure by follow-up interval, age at start of treatment, attained age, treatment category, and laterality

Characteristic	Myocardial infarction				Angina pectoris				Congestive heart failure			
	Obs	SIR	(95% CI)	AER*	Obs	SIR	(95% CI)	AER*	Obs	SIR	(95% CI)	AER*
Follow-up interval, y												
10–14	128	1.35	(1.13 to 1.61)	17.4	129	1.09	(0.91 to 1.29)	5.5	149	1.27	(1.08 to 1.50)	16.8
15–19	85	1.19	(0.95 to 1.47)	12.2	111	1.42	(1.17 to 1.71)	30.6	146	1.49	(1.26 to 1.76)	44.0
≥ 20	41	1.02	(0.73 to 1.38)	1.4	66	1.70	(1.31 to 2.16)	59.9	87	1.28	(1.03 to 1.59)	41.8
P_{trend}			.1				.002				.8	
Age at start of treatment, y												
< 45	32	1.11	(0.76 to 1.57)	2.8	63	1.67	(1.28 to 2.140	22.5	67	3.87	(3.00 to 4.92)	43.6
45–54	104	1.40	(1.14 to 1.69)	21.3	137	1.38	(1.16 to 1.63)	27.6	131	1.81	(1.51 to 2.15)	42.5
≥ 55	118	1.14	(0.94 to 1.37)	15.0	106	1.07	(0.88 to 1.30)	8.0	184	0.95	(0.82 to 1.10)	–9.6
P_{trend}			.6				.004				< .001	
Attained age, y												
< 55	11	1.25	(0.63 to 2.24)	3.5	17	1.40	(0.82 to 2.24)	7.9	24	4.25	(2.72 to 6.32)	29.7
55–64	65	1.46	(1.12 to 1.86)	16.5	94	1.39	(1.13 to 1.71)	22.0	78	2.85	(2.26 to 3.56)	41.4
≥ 65	178	1.16	(1.00 to 1.35)	15.0	195	1.25	(1.08 to 1.44)	24.7	280	1.12	(0.99 to 1.26)	18.8
P_{trend}			.2				.4				< .001	
Treatment												
Surgery only	23	0.68	(0.43 to 1.03)	–21.5	37	1.01	(0.71 to 1.39)	0.9	44	0.85	(0.61 to 1.14)	–16.7
RT (± surgery)	167	1.33	(1.14 to 1.55)	20.1	204	1.42	(1.23 to 1.63)	29.9	215	1.23	(1.07 to 1.40)	19.4
RT+CT (± surgery)	20	1.36	(0.83 to 2.10)	14.3	29	1.66	(1.12 to 2.40)	31.7	39	3.48	(2.48 to 4.76)	75.3
RT+HT (± surgery)	27	1.38	(0.91 to 2.02)	25.2	23	1.05	(0.66 to 1.57)	3.5	54	1.86	(1.40 to 2.43)	83.9
RT+CT+HT (± surgery)	12	1.19	(0.61 to 2.08)	8.6	13	0.99	(0.53 to 1.70)	–0.4	26	2.66	(1.74 to 3.90)	72.8
Laterality												
Left	122	1.22	(1.01 to 1.45)	12.8	149	1.31	(1.11 to 1.54)	21.5	184	1.37	(1.18 to 1.58)	29.8
Right	117	1.19	(0.98 to 1.43)	11.2	138	1.22	(1.03 to 1.44)	15.6	167	1.25	(1.07 to 1.46)	21.0

Abbreviations: Obs, observed number of events; SIR, standardized incidence ratio; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy. AER, absolute excess risk per 10,000 patients per year; y, years.

divided the cohort according to period of treatment (Figure 4.1). Because breast-conserving therapy was introduced at our institutions in 1980, we used this year as cutoff point for stratification. For the period 1970–1979, irradiated patients experienced a 1.49-fold higher risk of cardiovascular disease than non-irradiated patients, whereas for the period 1980–1986, the risk declined to 1.35 (and was not statistically significant). Only adjustment for age was needed—smoking, hypertension, diabetes mellitus, and hypercholesterolemia were independent risk factors and did not influence the risk estimates for radiotherapy. Any radiotherapy was associated with increased risks of both myocardial infarction (HR = 2.77; 95% CI: 1.62 - 4.75; P<.001) and congestive heart failure (HR = 1.47; 95% CI: 1.04 - 2.08; P=.03) compared with no radiotherapy for the treatment period 1970–1979, whereas these risks declined and were no

Table 4.5. Multivariate Cox regression analyses* of potential risk factors for myocardial infarction and congestive heart failure by treatment period

	Risk of myocardial infarction†				Risk of congestive heart failure†			
	1970–1979		1980–1986		1970–1979		1980–1986	
Risk Factor	**HR (95% CI)**	***P*‡**	**HR (95% CI)**	***P*‡**	**HR (95% CI)**	***P*‡**	**HR (95% CI)**	***P*‡**
Treatment								
RT vs no RT	2.77 (1.62 to 4.75)	< .001	0.87 (0.47 to 1.59)	.64	1.47 (1.04 to 2.08)	.03	1.39 (0.69 to 2.80)	.35
CT vs no CT	0.64 (0.29 to 1.41)	.27	1.22 (0.74 to 2.00)	.43	0.78 (0.45 to 1.37)	.39	1.85 (1.25 to 2.73)	.002
HT vs no HT	1.09 (0.70 to 1.71)	.70	1.16 (0.68 to 1.95)	.59	1.60 (1.16 to 2.20)	.004	1.23 (0.80 to 1.91)	.35
Smoking ever vs never through the end of follow-up	2.00 (1.42 to 2.83)	< .001	2.63 (1.51 to 4.59)	.001	1.39 (1.05 to 1.84)	.02	1.30 (0.75 to 2.25)	.35
ex-smoker	1.34 (0.79 to 2.29)	.28	1.35 (0.80 to 2.25)	.26	1.01 (0.66 to 1.57)	.96	1.04 (0.66 to 1.63)	.88
Hypertension, yes vs no/unknown	1.90 (1.35 to 2.66)	< .001	1.97 (1.29 to 3.01)	.002	1.35 (1.03 to 1.76)	.03	1.41 (0.96 to 2.05)	.08
Diabetes mellitus, yes vs no/unknown	1.20 (0.78 to 1.84)	.40	1.31 (0.78 to 2.21)	.31	1.13 (0.78 to 1.63)	.53	1.30 (0.80 to 2.11)	.29
Hypercholesterolemia, yes vs no/unknown	2.90 (1.96 to 4.28)	< .001	2.79 (1.81 to 4.32)	< .001	1.09 (0.72 to 1.65)	.68	2.30 (1.55 to 3.41)	< .001

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

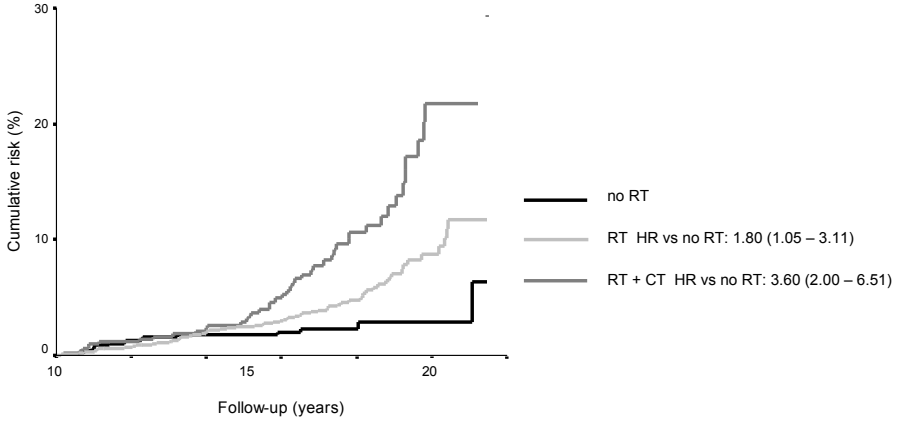
*Results from four Cox analyses: two separate models were run both for myocardial infarction and for congestive heart failure, with patients stratified by treatment period (1970–1979 and 1980–1986, respectively).

†Adjusted for age at breast cancer diagnosis; all presented variables were included in the model, although the cardiovascular risk factors did not influence the risk estimates for RT, CT or HT.

‡*P* value from Wald test statistic.

longer different from unity for the period 1980–1986 (Table 4.5). Furthermore, chemotherapy was associated with an increased risk of congestive heart failure for the treatment period 1980–1986 (HR = 1.85; 95% CI: 1.25 - 2.73; *P*=.002, Table 4.5, Figure 4.2). In a separate analysis that was restricted to primary treatment, risk of congestive heart failure remained increased for patients who received adjuvant chemotherapy during 1980–1986 (HR = 2.30; 95% CI: 1.44 - 3.67; data not shown in table).

Risks of myocardial infarction and congestive heart failure were also analyzed by region of irradiation (Table 4.6, Figures 4.3 and 4.4). For the period 1970–79, radiotherapy to the internal mammary chain was associated with an increased risk of myocardial infarction irrespective of tumor laterality (HR = 2.55) as compared with the referent group (patients treated without radiotherapy or with fields giving a negligible dose to the heart). For the treatment period 1980–86, these risks were close to unity. Compared with the referent group, patients who received radiotherapy to the left chest wall alone in the period 1970–1979 experienced an increased risk of myocardial infarction (HR = 2.72), whereas radiotherapy to the right chest wall showed a statistically nonsignificantly 1.76-fold increased risk. For the period 1980–1986, risk of myocardial infarction was not increased after chest wall or breast irradiation (Table 4.5). However, analysis using another Cox model specifically for radiotherapy to left chest wall



numbers at risk:

no RT	591	393	35
RT	1195	905	131
RT + CT	594	406	47

Figure 4.2. Risk of congestive heart failure by treatment group (Cox model), adjusted for age, for patients treated since 1980. RT = radiotherapy; CT = chemotherapy; HR = hazard ratio.

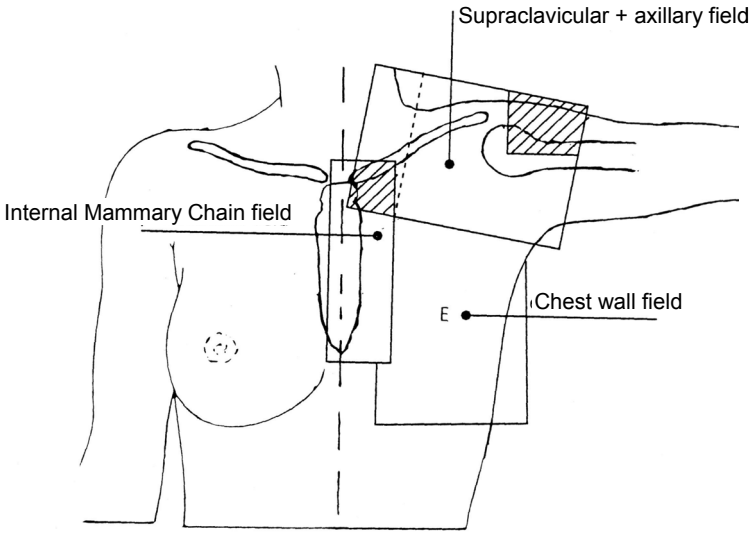


Figure 4.3. Locoregional radiotherapy fields following mastectomy

alone in this period, showed increased risk of myocardial infarction (HR = 3.54) versus the referent group (receiving no radiotherapy, or negligible dose to the heart). Risk of angina pectoris showed similar, although less pronounced, associations with the various radiotherapy fields.

We next examined risk of congestive heart failure by irradiated region. Radiotherapy to the internal mammary chain plus chest wall in the period 1970–79 was also associated with an increased risk of congestive heart failure for both left- and right-sided tumors (Table 4.6; HR =

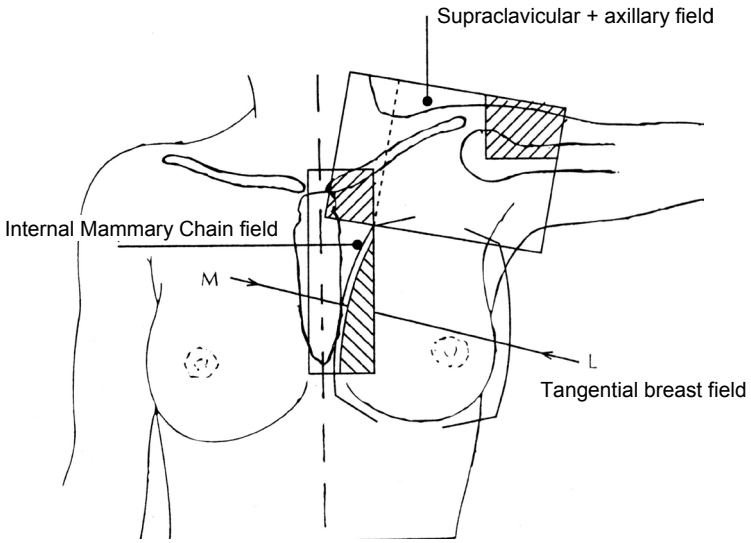


Figure 4.4. Locoregional radiotherapy fields following lumpectomy

2.29 and HR = 2.15, respectively), whereas radiotherapy to the internal mammary chain only was associated with marginally statistically significantly increased risks. For those treated in the period 1980–1986, the risk of congestive heart failure remained increased after irradiation of the internal mammary chain plus breast (irrespective of laterality, HR = 2.66; 95% CI: 1.27 - 5.61). We calculated rough estimates of mean cardiac dose for each region and the range in doses using various techniques (Table 4.6). In general, risk of congestive heart failure increased with higher mean dose of radiation to the heart. As for risk of myocardial infarction, the same trend with dose was observed in patients who were treated during 1970–1979, but not in patients from the later period of 1980–1986. Comparison of risks for patients treated with left- vs right-sided radiation fields (Table 4.7) only showed a statistically nonsignificant increase in left/right ratio of risk of myocardial infarction (HR = 1.77) and congestive heart failure (HR = 1.41) after chest wall field irradiation.

We also examined the association of radiotherapy on risk of valvular dysfunction. Irrespective of the treatment period, patients who had radiotherapy to the internal mammary chain for both left- and right-sided tumors experienced an increased risk of valvular dysfunction, (HR = 3.17; 95% CI: 1.90 - 5.29). Risk of dysrhythmias was not associated with any radiotherapy field.

Analyses stratified by follow-up time showed that the radiotherapy-associated risk of cardiovascular disease increased with longer follow-up (for myocardial infarction during the 10–20 year and >20 year follow-up intervals, HR = 1.5 and HR = 1.8, respectively, P_{trend} = .03, and for congestive heart failure, HR = 1.6 and HR = 2.1, respectively, P_{trend} <.001).

Table 4.6. Multivariable Cox regression analyses* for myocardial infarction and congestive heart failure, by RT field and estimated mean radiation dose to the heart by treatment period

Treatment period	No. of patients	Estimated mean heart dose, Gy	Dose range, Gy	Myocardial infarction		Congestive heart failure	
				HR (95% CI) †	*P*‡	HR† (95% CI)	*P*‡
1970–1979							
RT fields							
no RT/ fields not including heart§	431	≈0	≈0	1.0 (referent)		1.0 (referent)	
chest wall/breast: right-sided	179	≈3	1.2–3.8	1.76 (0.88 to 3.51)	.11	0.96 (0.57 to 1.63)	.89
chest wall/breast: left-sided	168	≈7	2.5– 9.0	2.72 (1.38 to 5.38)	.004	1.10 (0.64 to 1.92)	.73
IMC only: right-sided	348	≈7	0.5–11.6	2.59 (1.46 to 4.61) ‖	.001	1.44 (0.94 to 2.20)#	.10
IMC only: left-sided	386	≈9	0.7–15.6	2.00 (1.12 to 3.58) ‖	.02	1.61 (1.08 to 2.41)#	.02
IMC + chest wall/breast: right-sided	158	≈11	2.7–15.4	4.77 (2.43 to 9.35) ‖	< .001	2.15 (1.28 to 3.60)#	.004
IMC + chest wall/breast: left-sided	166	≈15	4.7–18.3	2.59 (1.29 to 5.18) ‖	.007	2.29 (1.44 to 3.65)#	< .001
1980–1986							
RT fields							
no RT/ fields not including heart§	261	≈0	≈0	1.0 (referent)		1.0 (referent)	
breast/ chest wall: right-sided	316	≈1.5	1.2–1.6	0.71 (0.29 to 1.74)	.46	0.80 (0.28 to 2.29)	.68
breast/ chest wall: left-sided	395	≈5	2.5–5.3	0.79 (0.36 to 1.72)¶	.55	1.16 (0.48 to 2.79)	.75
IMC only: right-sided	359	≈6	0.5–11.6	0.95 (0.46 to 1.93)	.88	1.43 (0.65 to 3.16)	.38
IMC only: left-sided	346	≈7	0.7–15.6	0.94 (0.46 to 1.91)	.86	1.81 (0.84 to 3.92)	.13
IMC + breast/ chest wall: right-sided	365	≈9	2.5–14.0	0.80 (0.36 to 1.78)	.58	2.82 (1.27 to 6.29)**	.01
IMC + breast/ chest wall: left-sided	376	≈13	4.0–19.9	0.67 (0.30 to 1.52)	.34	2.52 (1.13 to 5.62)**	.02

Abbreviations: HR, hazard ratio; CI, confidence interval; RT, radiotherapy; IMC, internal mammary chain.

*Results from four Cox analyses: two separate models were run both for myocardial infarction and for congestive heart failure, with patients stratified by treatment period (1970–1979 and 1980–1986, respectively).

†Adjusted for age at breast cancer diagnosis, chemotherapy, hormonal therapy, and the cardiovascular risk factors.

‡*P* value from Wald test statistic.

§Fields not including heart: no IMC, chest wall, or breast.

‖ Risk of myocardial infarction: for any IMC-RT given between 1970 and 1979, irrespective of laterality, HR, 2.55; 95% CI: 1.55 - 4.19 (*P*<.001).

¶Risk of myocardial infarction: for left-sided chest wall RT given between 1980 and 1986, HR, 3.54; 95% CI: 1.13 - 11.1 (*P*=.03).

#Risk of congestive heart failure: for any IMC-RT given between 1970 and 1979, irrespective of laterality, HR, 1.72; 95% CI: 1.22 - 2.41 (*P*=.002).

**Risk of congestive heart failure: for IMC + breast RT given between 1980 and 1986, irrespective of laterality, HR, 2.66; 95% CI: 1.27 - 5.61 (*P*=.01).

Table 4.7. Risks of myocardial infarction and congestive heart failure by RT field from multivariable Cox regression analysis

RT fields	Myocardial infarction		Congestive heart failure	
	HR (95% CI)	*P**	HR (95% CI)	*P**
IMC, left vs right	0.87 (0.59 to 1.29)	.49	1.16 (0.84 to 1.60)	.37
Chest wall, left vs right	1.77 (0.91 to 3.43)	.09	1.41 (0.76 to 2.61)	.28
Breast, left vs right	0.74 (0.31 to 1.79)	.51	1.01 (0.40 to 2.55)	.99

Abbreviations: RT, radiotherapy; HR, hazard ratio; IMC, internal mammary chain.
**P* value from Wald test statistic.

Table 4.8. Multivariable Cox regression analysis: combined effects of RT and cardiovascular risk factors on myocardial infarction*

Risk Factor	No RT			RT			
	No. of patients at risk	No. of events	HR† (95% CI)	No. of patients at risk	No. of events	HR† (95% CI)	*P*‡
Smoking§							
No	797	43	1.00 (ref.)	2072	113	1.34 (0.94 to 1.91)	
Yes	231	11	1.36 (0.69 to 2.68)	737	61	3.04 (2.03 to 4.55)	.039
Hypercholesterolemia							
No	1127	45	1.00 (ref.)	2780	134	1.59 (1.13 to 2.24)	
Yes	120	18	3.11 (1.78 to 5.42)	315	57	4.62 (3.06 to 6.98)	.36
Hypertension							
No	894	24	1.00 (ref.)	2302	95	1.92 (1.22 to 3.01)	
Yes	353	39	2.49 (1.49 to 4.16)	793	96	3.31 (2.09 to 5.24)	>.50
Diabetes mellitus							
No	1123	45	1.00 (ref.)	2843	160	1.81 (1.29 to 2.53)	
Yes	124	18	2.01 (1.15 to 3.53)	252	31	1.87 (1.17 to 3.00)	.12
History of IHD							
No	1222	59	1.00 (ref.)	3044	181	1.56 (1.16 to 2.11)	
Yes	25	4	1.53 (0.54 to 4.32)	51	10	2.31 (1.15 to 4.65)	>.50

Abbreviations: RT, radiotherapy; HR, hazard ratio; CI, confidence interval; ref, reference group = 1.0, for background risk; IHD, ischemic heart disease.

*Biologic interaction was evaluated as departure from additivity of the effect of two risk factors, where the 'interaction risk' is the risk that cannot be explained by the joint exposure to both risk factors, as expressed in the formula: $R_{INT} = R_{A+B} - (R_A + R_B - R_U)$. For example, R_A = risk of MI from smoking; R_B = risk of MI from RT; R_{A+B} = risk of MI from smoking and RT together; R_U = background risk of MI = 1.0. In the formula: $R_{INT} = 3.04 - (1.36 + 1.34 - 1.0) = 1.34$.

†HR adjusted for age at breast cancer diagnosis, treatment period, smoking, hypercholesterolemia, hypertension and diabetes mellitus.

‡P value for departure from additivity, derived from likelihood ratio test statistic.

§Total of 505 patients with unknown smoking status excluded from analysis.

Analysis of the combined effects of radiotherapy and various cardiac risk factors (Table 4.8) revealed a more than additive effect of the combination of radiotherapy and smoking on myocardial infarction risk (HR = 3.04; 95% CI: 2.03 - 4.55; $P_{\text{departure from additivity}} = .039$).

Discussion

After a median follow-up of almost 18 years, we found an association between increased risk of cardiovascular disease and internal mammary chain irradiation for both left- and right-sided breast cancer in the period 1970–1979. For those treated during 1980–1986, the risk of myocardial infarction after internal mammary chain (plus breast) irradiation declined towards unity, but the risk of congestive heart failure remained increased. Internal mammary chain radiotherapy was also associated with an increased risk of valvular dysfunction. Irradiation of the left but not the right chest wall was associated with an increased risk of myocardial infarction for the entire treatment period 1970–1986. After a median follow-up of more than 16 years, the risks of myocardial infarction and congestive heart failure were not increased in patients who received radiotherapy to the breast only. Surprisingly, patients who were treated with radiotherapy plus adjuvant CMF experienced a statistically significantly increased risk of congestive heart failure compared with those treated with radiotherapy alone. Remarkably, the combined effects of radiotherapy and smoking on myocardial infarction risk were more than additive. To our knowledge, our study is the first to examine the effects of combined exposure to radiotherapy and cardiovascular risk factors.

To date, most studies have focused on cardiac mortality, and only a few have reported on morbidity.[8,9,11,24] Few risk estimates for cardiac disease after radiation to specific fields have been published, and radiation doses to the heart were not estimated in previous reports. Therefore, our results may explain some of the inconsistencies raised by previous studies. There is little debate regarding the radiotherapy-related risk of cardiac disease imposed by the older radiotherapy regimens from the 1960s and 1970s.[2-5] In the last update of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on local therapy, comparison of cardiovascular mortality between patients treated with and without radiotherapy yielded a statistically significant rate ratio of 1.27.[4] Studies on cardiovascular risk following more modern regimens from the 1980s, however, have had inconclusive results, possibly because of differences in the types of radiotherapy fields used, the methodology used to compare left- versus right-side–associated risks, the size of the studies, the duration of follow-up, and the definition of endpoints. In many studies of radiotherapy-related cardiovascular mortality, risk is compared between left- and right-sided tumors, as a surrogate for cardiac exposure to radiation.[6-10,24-26] Patients who have left-sided breast cancer and are treated with radiation to the chest wall generally receive a higher dose of radiation to a larger volume of cardiac tissue than patients with right-sided disease. However, the left-right difference in cardiac exposure to radiation can be less evident in case of internal mammary chain irradiation through a separate anterior field.[27] Estimation of mean radiation dose to the heart in our study indeed showed that the difference between left- and right-sided irradiation was relatively small for internal mammary chain-irradiation (Table 4.6). Consequently, information on the regimens used is required to decide whether a left-right comparison is meaningful.

In our study, many patients received internal mammary chain radiation using an anterior field, and we only found a slightly statistically nonsignificantly increased risk of cardiovascular disease (HR = 1.1) for left- versus right-sided tumors. This left- versus right-sided comparison did not reveal that the true risk increase due to radiotherapy was higher (HR = 1.4; 95% CI: 1.1 - 1.7) when compared with surgery only. Likewise, Vallis et al.[9], Rutqvist et al.[8], and Nixon et al.[6] did not find excess risks of cardiovascular disease among patients who received irradiation of the left breast, with regional nodal areas irradiated in less than 6%, 12%, and 80% of the patients, respectively. Interpretation of these results is difficult, however, because the studies analyzed only few cardiac events. Furthermore, follow-up time was fairly short for an increase of cardiovascular disease risk to become manifest. This was also the case in the study by Højris et al.[11], which compared patients in Denmark who were treated during 1982–1990 with or without postmastectomy radiation (including the ipsilateral internal mammary chain field) and found no increased risk of cardiovascular disease among the irradiated patients. Conversely, in two large population-based studies,[7,10] statistically significantly increased risks of cardiac death were associated with left-sided tumors (2.1 and 1.1, respectively). Based on the 1973–2000 dataset from the Surveillance, Epidemiology and End Results (SEER) cancer registries, Giordano et al.[25] also found a statistically significant increase of cardiac mortality among patients with left-sided tumors who were treated with radiation therapy in the period 1973–1979 (for 1979, HR = 1.5), whereas after 1979, the difference in risk between patients with left- and right-sided tumors declined to unity. Also based on the SEER dataset but with longer follow-up, a recent study by Darby et al.[26] showed increased cardiac mortality ratios (left- versus right-sided tumors) for patients who were treated with radiation therapy during 1973–1982 and decreasing ratios for patients treated from 1983 onward. In the last four studies,[7,10,24,25] no information was available on the proportion of patients who received radiation treatment to the regional lymph nodes.

Most previous studies of cardiovascular disease risk after breast cancer treatment evaluated risk of ischemic heart disease, except for that of Patt et al.[24], who also reported on risk of valvular heart disease, congestive heart failure, and conduction abnormalities. They found no statistically significant differences in cardiac morbidity after radiation for left- versus right-sided breast cancer among patients who were treated between 1986 and 1993. However, mean follow-up was only 9.5 years. Among Hodgkin lymphoma survivors who were treated with radiotherapy, valvular dysfunction at a median of 22 years after first treatment has been described.[28] Our study showed associations not only between radiation therapy and increased risks of ischemic heart disease but also between radiation treatment and valvular dysfunction and congestive heart failure. Thus, many cardiac events may be missed by restricting study outcome to ischemic heart disease.

A remarkable finding in our study was that chemotherapy was associated with increased risk of congestive heart failure. The risk associated with chemotherapy was increased even more in the analysis that was restricted to primary treatment only, indicating an association

with CMF, the standard adjuvant chemotherapy regimen during the study period. We can only speculate on the mechanisms involved, assuming the association is causal. Treatment with high doses of cyclophosphamide has been associated with increased risk of congestive heart failure. An increased risk could also be mediated through preliminary menopause from CMF, resulting in lower estrogen levels. However, we cannot rule out chance or undetected confounding as an explanation. Nor can we exclude a residual effect of radiotherapy that cannot be controlled for effectively because all patients who are treated with chemotherapy also received radiotherapy.

To date, no study of radiation therapy for breast cancer and cardiovascular disease has incorporated cardiovascular risk factors into its analysis. A recent study of coronary heart disease after radiotherapy for peptic ulcer disease[29] found that radiotherapy and smoking were independently associated with cardiovascular disease risk. In a study of Hodgkin lymphoma patients[30], no differences were found in radiotherapy-associated risk of myocardial infarction by history of smoking. Information on smoking was incomplete, however, which may have impaired the interaction analysis. We found that the joint associations between radiotherapy and smoking and myocardial infarction risk were greater than expected when individual risks were summed. Consequently, the advice to stop smoking appears to be even more important for irradiated patients and should be given at the time of treatment.

When interpreting our results, the strengths and limitations of our study should be considered. Unlike most studies, we collected information on all primary and follow-up treatments, including radiation fields and cardiovascular disease risk factors. Follow-up was nearly complete and very long, with more than 30% of patients followed for more than 20 years.

A potential limitation of our study is the assumption that the population-based incidence rates for cardiac disease are an appropriate comparison group in the person-years analysis. In this analysis, we accounted for age and calendar year during follow-up, but we cannot exclude potential differences in cardiac risk profiles between the study group and the reference population. It is possible that patients included in our study may have begun a healthier lifestyle after breast cancer diagnosis. Also, in this hospital-based study population, we may have selected breast cancer patients with higher socioeconomic status than the general population. Nevertheless, these differences would result in an underestimation of the true cardiac risk as compared with a general population sample with similar characteristics. This potential limitation relates only to our general population comparisons and not to the Cox model analyses.

Surveillance bias is highly unlikely in our patient population because the majority of patients were discharged from routine follow-up in the cancer center 10 years after breast cancer diagnosis. Also, although radiotherapy-related risk of cardiovascular disease has been known for a long time, we know from the medical records of patients in the study that irradiated patients were not routinely screened for cardiac symptoms. This lack of screening was also confirmed in a pilot study showing that 20% of the cardiovascular events reported by the

general practitioners were not registered in our oncologic records. Furthermore, as we reported earlier in an analysis of cause-specific mortality in this cohort[12], we also found increased mortality of cardiovascular disease in irradiated patients (standardized mortality ratio [SMR] = 1.12; 95% CI: 0.95 - 1.30) compared with patients who were treated with surgery only (SMR = 0.54; 95% CI: 0.35 - 0.80; for irradiated versus non-irradiated patients, RR = 2.07; 95% CI: 1.35 - 3.29). Finally, the reference rates used to generate population-expected values as well as the observed events were both obtained from general practitioners. Therefore, confounding from using different sources to obtain observed and expected rates is highly unlikely.

Our choice for the surgery-only group as a reference group in the Cox regression analysis is a possible limitation if patients who were treated with surgery alone had a different cardiovascular risk profile than that of other treatment groups. This seemed to be the case in several population-based studies[7,10,24-26] and was a motivation for comparison of cardiac risks between irradiated patients with left- and right-sided tumors in those studies, excluding patients who were treated with surgery only. We believe that confounding by contraindication in general occurs only in older patients who have comorbid conditions.[31,32] In our study, patients who were older than 70 years were excluded, and we did not observe patient selection for treatment. In both cancer centers, treatment decisions regarding radiotherapy were not affected by either socioeconomic status, distance to the cancer center (data not shown), or the presence of cardiac disease. Even among patients who had a history of cardiovascular disease or hypertension at the time of breast cancer diagnosis (n = 528), 95.0% of patients for whom radiotherapy (axillary node involvement and/or medially located tumor) was prescribed were indeed treated, compared with 95.1% of patients without these risk factors.

Possible relationships between cardiovascular disease risk and irradiated volume of the heart or dose per fraction as assessed by others[7,33] could not be evaluated in our cohort because not all required data were collected. We could, however, roughly estimate the mean cardiac doses received in various periods from different fields and techniques. The range of doses per field was wide, and, thus, the increased risk of cardiovascular disease observed in a category with estimated low mean cardiac dose may reflect a subgroup of patients who received relatively high cardiac doses. Furthermore, the clear reduction in myocardial infarction risk for patients treated in 1980–1986, with mean cardiac radiation doses that were only slightly lower than in the earlier period, could arise if the relevant exposure parameter is radiation dose to the left anterior descending coronary artery or the percentage of the heart exposed to 5 Gy or more.

Overall, however, the risk of cardiovascular disease increased with increasing mean cardiac dose. The decline in risk observed for the more recent treatment period is consistent with recently published studies. Whether the excess risk has disappeared completely remains to be determined. During the 1990s, the use of internal mammary chain irradiation was drastically reduced, but it may still be used in patients with positive internal mammary chain

nodes as diagnosed by the sentinel node procedure or in patients with a high number of tumor-positive axillary nodes. As a consequence, a sizable and growing patient population is at increased risk of cardiovascular disease. Yet, we should remember the rationale for administering adjuvant radiotherapy in the first place: the last meta-analysis of the EBCTCG on the reduced risk of local recurrence after radiotherapy[4] concluded that, in the hypothetical absence of other causes of death, approximately one breast cancer death during the next 15 years would be avoided for every four local recurrences avoided.

In conclusion, apart from the clear benefits of adjuvant radiotherapy, physicians should be still aware of the potentially increased risk of cardiovascular disease following specific radiotherapy regimens in long-term breast cancer survivors. Radiotherapy to the left and right internal mammary chains was associated with equally increased risks of congestive heart failure, whereas irradiation of the left chest wall was associated with increased risk of myocardial infarction. Irradiation of the breast only, with the heart receiving minimal exposure, was not associated with an increased risk of cardiovascular disease. Apart from radiotherapy, adjuvant CMF was also associated with increased risk of congestive heart failure. To our knowledge, this late adverse effect from non–anthracycline-containing chemotherapy has not been reported before and warrants further research. The greater than additive magnitude of smoking and radiotherapy on risk of myocardial infarction stresses the need to advise irradiated patients even more urgently to refrain from smoking. Clearly, more prolonged follow-up of large cohorts will be needed to further evaluate the long-term risks and benefits of modern adjuvant radiotherapy and chemotherapy for early breast cancer.[1,3,4]

Acknowledgment

We thank E.H. van de Lisdonk from CMR–Nijmegen for supplying us with incidence rates of cardiovascular diagnoses; A.A.M. Hart, M. Hauptmann and W.J. Klokman (The Netherlands Cancer Institute, Amsterdam) for statistical advice; N.S. Russell (The Netherlands Cancer Institute, Amsterdam) for comments on radiation techniques, A.W. van den Belt–Dusebout, V.B. Hartog, M.A. Kuenen and the hospital cancer registries of the Netherlands Cancer Institute and the Erasmus MC, Daniel den Hoed Cancer Center for assistance in data collection. This study would not have been possible without the collaboration of more than 3000 physicians from throughout the Netherlands who provided follow-up data.

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5 Decreased risk of stroke among 10-year survivors of breast cancer

Maartje J. Hooning*, Lucille D.A. Dorresteijn*, Berthe M.P. Aleman, Arnoud C. Kappelle, Jan G.M. Klijn, Willem Boogerd, Flora E. van Leeuwen

*Both authors contributed equally to this work.

J Clin Oncol 2006; 24(34): 5388-94.

Abstract

Purpose

To assess treatment-specific risk of cerebrovascular events in early breast cancer (BC) patients, accounting for cerebrovascular risk factors.

Patients and methods

We studied the incidence of cerebrovascular disease (CVA; stroke and transient ischemic attack [TIA]) in 10-year survivors of early BC (n = 4414) treated from 1970 to 1986. Follow-up was 96% complete until January 2000. Treatment-specific incidence of CVA was evaluated by standardized incidence ratios (SIRs) based on comparison with general population rates and by Cox proportional hazards regression.

Results

After a median follow-up of 18 years, 164 strokes and 109 TIAs were observed, resulting in decreased SIRs of 0.8 (95% confidence interval [CI], 0.6 - 0.9) for stroke and 0.8 (95% CI: 0.7 - 1.0) for TIA. Significantly increased risk of stroke was found in women who had received hormonal treatment (HT; tamoxifen), and in women who had hypertension or hypercholesterolemia, with hazard ratios (HRs) of 1.9, 2.1, and 1.6, respectively. Patients irradiated on the supraclavicular area and/or internal mammary chain (IMC) did not experience a higher risk of stroke (HR = 1.0; 95% CI: 0.7 - 1.6) or TIA (HR = 1.4; 95% CI: 0.9 - 2.5) compared with patients who did not receive radiotherapy or who were irradiated on fields other than supraclavicular area or IMC.

Conclusions

Long-term survivors of BC experience no increased risk of cerebrovascular events compared with the general population. HT is associated with an increased risk of stroke. Radiation fields including the carotid artery do not seem to increase the risk of stroke compared with other fields.

Introduction

The prognosis of patients with early breast cancer (BC) has significantly improved over the past decades as a result of earlier diagnosis and the use of multimodality treatment. Meta-analyses of randomized clinical trials by the Early Breast Cancer Trialists' Collaborative Group have shown an important reduction in local recurrence rate and in BC mortality as a result of the application of postoperative adjuvant radiotherapy (RT)[1-3] and adjuvant systemic therapy.[4] However, adjuvant RT has also been associated with increased risks of cardiovascular morbidity and second primary cancers.[5-7] Exposure to chemotherapy or hormonal therapy (HT) may even further increase the risk of cardiovascular disease.[8,9]

In BC patients treated with adjuvant RT, the coronary arteries, brachiocephalic trunk, subclavian artery, and common carotid arteries (CCAs) may be exposed, depending on the fields applied. As a result, BC patients are potentially at risk for late vascular sequelae of RT.[10-14] So far, nearly all studies on vascular sequelae after BC irradiation have focused on the risk of cardiac disease. RT-related stroke is mediated by accelerated atherosclerosis that can result in enhanced thromboembolism and stenosis of the area of the carotid artery within the RT portal.[15,16] Head and neck cancer patients and survivors of Hodgkin's lymphoma treated with local RT on the neck experience an increased risk of stroke during long-term follow-up.[17-19] In case of irradiation on the supraclavicular lymph nodes, the proximal part of the CCA is located within the RT portal. Therefore, we hypothesize that BC patients irradiated at the supraclavicular lymph nodes are subject to an increased risk of stroke.

Until now, no study has reported on the incidence of ischemic stroke in relation to specific radiation regimens for BC. Therefore, we examined the incidence of cerebrovascular accident (CVA) in the Dutch Late Effects Breast Cancer cohort. Unique features of this study include near-complete and long-term follow-up (median, 18 years), the assessment of cerebrovascular risk according to radiation field, and the incorporation of cerebrovascular risk factors into the analysis.

Patients and methods

Data collection procedures

The Late Effects Breast Cancer cohort consists of 7425 1-year survivors, younger than 71 years of age at diagnosis, treated for stage I, II, or IIIA female BC in the period from 1970 to 1986 in the Netherlands Cancer Institute or the Erasmus MC, Daniel den Hoed Cancer Center. A detailed description of data collection procedures has been published previously.[20] In brief, all patients were identified through the hospital-based cancer registries of the two centers. From the registries and the oncologic records, we collected the following information: date of BC diagnosis, tumor histology, axillary lymph node involvement, dates and treatment modalities

of primary BC and of recurrent disease (i.e., type of surgery, radiation fields, cytostatic agents, and HT), dates of stroke and transient ischemic attack (TIA), cerebrovascular risk factors, date of most recent medical information or date of death and primary cause of death. Risk factors (such as smoking, hypertension, diabetes mellitus [DM], and hypercholesterolemia) were recorded both at the date of diagnosis of BC and at the end of follow-up. Smoking was scored positive when the patient was currently smoking or had stopped smoking less than 1 year before. Hypertension, hypercholesterolemia and DM were scored as positive when stated in the medical information or when treated.

We restricted this study to patients who survived BC for at least 10 years (n = 4414) because the increase in risk of vascular events associated with RT seems to emerge after 10 or more years.[2,5,15-17,20] For these patients, we updated information until at least January 1, 2000 on cerebrovascular diagnoses and risk factors by sending questionnaires to their general practitioners (GPs). In The Netherlands, nearly all residents have a GP who receives all medical correspondence from attending physicians. Forty-six patients were excluded from the cohort because their oncologic records did not contain information after 10 years since diagnosis and no additional information on vascular events could be obtained from their GPs. For the remaining 4368 patients, we collected cerebrovascular data for 83% of the patients from both the medical record and the GP, and for the other 17% of patients, we collected data from the oncologic records only. Complete follow-up information was eventually available for 4259 patients (96%). For patients who died from a stroke, without prior evidence of a cerebrovascular event, the date of death was recorded as date of diagnosis of stroke.

Treatment

During the 1970s, standard treatment for stage I, II, and IIIA BC was modified or radical mastectomy with or without RT. As of 1975, adjuvant systemic treatment was introduced for node-positive patients, including combination chemotherapy for premenopausal patients and, gradually from 1980 onwards, tamoxifen for postmenopausal patients. Standard adjuvant chemotherapy consisted of cyclophosphamide, methotrexate and fluorouracil during the whole study period. In 1980, breast-conserving therapy was introduced in both hospitals. The RT regimen depended on type of surgery and stage of disease. In both hospitals, irradiation of the ipsilateral internal mammary chain (IMC) field was common for patients with centrally or medially located tumors and/or axillary lymph node metastases. The dose in the IMC varied from 40 Gy in 15 fractions in 3 weeks to 50 Gy in 25 fractions, using either photon beams or a mixture of photons and electrons. In case of extensive axillary nodal metastases, the axilla and supraclavicular nodes were irradiated as well (50 Gy in 25 fractions). In case of irradiation of the IMC including the medial supraclavicular nodes or of the supraclavicular nodes, the dose in the proximal part of the CCA was estimated between 80 and 100% of the total dose (equivalent of 40 to 50 Gy in fractions of 2 Gy, Figures 5.1a, 5.1b).

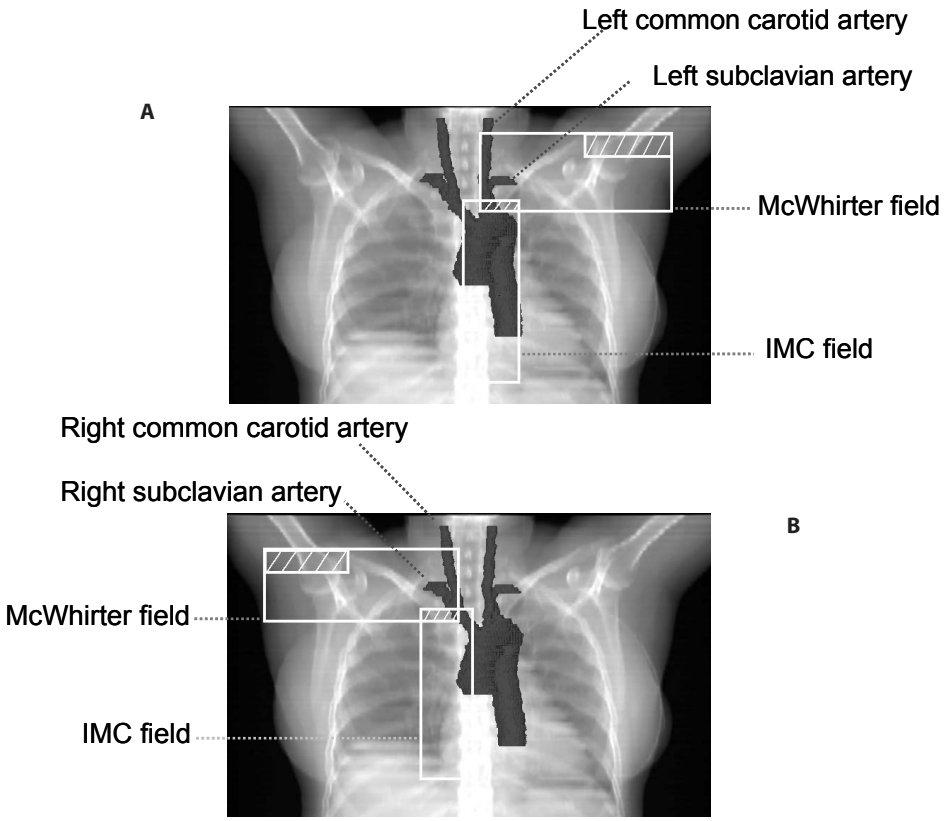

Figure 5.1. Schematic representation of the radiotherapy portal of the internal mammary chain field and the McWhirter (= supraclavicular + axillary) field in case of a) left-sided breast cancer and b) right-sided breast cancer. The estimated radiation dose at both the left and right common carotid artery is 40-50 Gy.

Statistical analysis

We compared the incidence of stroke and TIA in the study population with the incidence in the Dutch female population, taking into account the person-years of observation in the cohort (by age, calendar period, and follow-up interval). Incidence data of the Continuous Morbidity Registration–Nijmegen, derived from several GP practices from representative regions in The Netherlands, were used as reference rates.[21] This registry has collected data on the incidence of vascular events (including TIA) for the period from 1972 to 2000, allowing for multiple separate diagnoses per person but recording only the first of a specific diagnosis per person. To assess treatment effects on stroke risk, we distinguished five mutually exclusive treatment categories based on all treatments received (Table 5.1). Treatments administered in the last year of follow-up were excluded from the analysis because we did not want to take into account all salvage treatments received for recurrent disease during the last period in life. We also analyzed the effects of specific RT fields.

Table 5.1. Characteristics of 10-year survivors in the Dutch Late Effects BC Study

	Characteristic	No. of BC patients	%
No. of patients		4368	100
Hospital	NKI	2045	46.8
	DDHK	2323	53.2
Age at BC diagnosis (years)	< 45	1379	31.6
	45 - 54	1681	38.5
	≥ 55	1308	29.9
Year of first treatment of BC	1970 - 75	1075	24.6
	1976 - 80	1059	24.2
	1981 - 86	2234	51.1
Axillary node involvement (at diagnosis)	Node negative	2557	58.5
	Axillary node pos., subclav. neg.	1544	35.3
	Subclav. pos.	164	3.8
	Unknown	103	2.4
Laterality	Left	2229	51.0
	Right	2097	48.0
	Bilateral	42	1.0
Treatment category, primary + follow-up treatment	Surgery only	516	11.8
	RT (+ surgery)	2362	54.1
	RT + CT (+ surgery)	529	12.1
	RT + HT (+ surgery)	438	10.0
	RT + CT + HT (+ surgery)	448	10.3
	Other/unknown	75	1.7
Radiation fields, primary + follow-up treatment*	IMC	2538	58.1
	Chest wall	880	20.1
	Breast	1319	30.2
	Supraclavicular	1061	24.3
	Axilla	1356	31.0
Radiation fields, primary + follow-up treatment**	IMC, no supraclavicular	1712	39.2
	Supraclavicular, no IMC	227	5.2
	IMC + supraclavicular	826	18.9
	Other fields; but no IMC or supraclavicular	934	21.4
	Unknown	60	1.4
Follow-up time (years)	10 - 14	1081	24.7
	15 - 19	1917	43.9
	≥ 20	1370	31.4

Abbreviations: BC, breast cancer; NKI, Netherlands Cancer Institute; DDHK, Erasmus MC, Daniel den Hoed Cancer Center; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.

*Allowing more than one field per patient.

** Mutually exclusive treatment groups.

Follow-up time was defined as the period from the date of first treatment until the date of most recent medical information (including date of death). Because the study was restricted to 10-year survivors, time at risk began 10 years after the start of first treatment and ended at date of diagnosis of stroke or TIA, date of death, or date of most recent medical information, whichever came first. Observed numbers were based on all first events of stroke and TIA occurring during time at risk (i.e., after at least 10 years since first treatment); patients diagnosed with a cerebrovascular event before BC diagnosis or within 10 years since first treatment were excluded from the analysis. The standardized incidence ratios (SIRs) of the observed and expected numbers of stroke and TIA in the study population were determined, and the confidence intervals of the SIRs were calculated using exact Poisson probabilities of observed numbers.[22] *P* values for tests for trend were calculated according to standard methods. Absolute excess risk was calculated by subtracting the expected number of cerebrovascular events in our cohort from the number observed and dividing by person-years at risk (expressed per 10,000 person-years).

The Cox proportional hazards model[23] was used to quantify the effects of different treatments on the risk of CVA, taking into account several covariates. To evaluate the independent effects of primary adjuvant treatment, we did a separate analysis where time at risk ended at date of treatment for recurrent disease. Cox models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

The median age at BC diagnosis in the study population was 49 years, and 32% of patients were younger than 45 years at diagnosis (Table 5.1). Median follow-up time was 17.7 years, and 31% of the patients were followed for more than 20 years. Fifty-four percent of the patients were treated with a combination of RT and surgery, and 32% received RT and adjuvant chemotherapy and/or HT, the latter mostly for recurrent disease. Fifty-eight percent of patients received IMC RT, usually including the medial supraclavicular area, 50% were irradiated to the chest wall or breast region, and 24% were irradiated to the supraclavicular area.

Table 5.2 displays the information on cerebrovascular risk factors in the study population. We compared the distribution of hypertension, DM, and hypercholesterolemia by age categories in our study to the reference population from CMR–Nijmegen (Table 5.3). Since this Registry had no data on smoking habits, we used figures from a nationwide survey held in 2000 for comparison.[24] At the end of follow-up, the distribution of risk factors was very similar in our study group compared with the control population, with the exception of patients aged more than 75 years, who had a significantly higher prevalence of hypertension (44% versus 34%, respectively; $P < 0.001$)

Table 5.2. Risk factors for stroke or TIA in 10-year survivors of the Dutch Late Effects BC Study

		No. of patients	%
Smoking:	Never	2136	48.9
	Unknown at BC diagnosis, but not at end of follow-up	334	7.6
	Smoking at BC diagnosis, but not anymore at end of follow-up	413	9.5
	Smoking at BC diagnosis, unknown at end of follow-up	551	12.6
	Smoking through the end of follow-up	426	9.8
	Unknown	508	11.6
Hypertension:	No	3039	69.5
	Diagnosed prior to BC diagnosis	444	10.2
	Developed during follow-up	716	16.4
	Unknown	169	3.9
Diabetes Mellitus:	No	3826	87.6
	Yes	383	8.8
	Unknown	159	3.6
Hypercholesterolemia:	No	3739	85.6
	Yes	441	10.1
	Unknown	188	4.3
History* of stroke/TIA:	No/ Unknown	4355	99.7
	Yes	13	0.3

Abbreviations: BC, breast cancer; TIA, transient ischemic attack.

*Before BC diagnosis.

Risk of CVA by age, follow-up and treatment regimen

Overall, we observed 164 strokes and 109 TIAs (Table 5.4), including 14 patients with both (TIA preceding stroke). In total, 51 patients died from a stroke. The median age at stroke diagnosis was 75.5 years after a median follow-up of 17.0 years; TIAs were diagnosed at a median age of 73.1 years after a median follow-up of 16.8 years.

With 217.6 strokes expected versus 164 seen, the risk of stroke was significantly decreased by 25% (SIR = 0.75; 95% CI: 0.64 - 0.88, Table 5.4). Decreased risk of stroke was found for all age groups. For TIA, the risk was increased in patients younger than 45 years old at BC diagnosis, with SIRs showing a consistent decline with older ages at diagnosis of BC (P for trend < 0.0001; Table 5.4). There was no trend over follow-up time for risk of stroke or TIA.

Risks of stroke and TIA did not differ between patients who were treated with surgery alone and those who received RT in combination with surgery. However, among patients who were treated with RT plus HT, we observed an elevated risk of stroke (SIR = 1.31; 95% CI: 0.87 - 1.88) compared with the general population, whereas risk of TIA was significantly increased in patients treated with RT plus chemotherapy (SIR = 2.90; 95% CI: 1.45 - 5.19).

Table 5.3. Distribution of risk factors (in %) by age categories

Smoking:	Late effects BC study	Dutch population
Age in 2000:	%	%
35 - 49	36	37
50 - 64	28	28
>= 65	15	15
Hypertension:	Late effects BC study	CMR Nijmegen
Age in 2000:	%	%
< 45	2	2
45 – 64	17	13
65 – 74	34	31
>= 75	44	34
Diabetes mellitus:	Late effects BC study	CMR Nijmegen
Age in 2000:	%	%
< 45	0.7	0.4
45 – 64	4	4
65 – 74	11	11
>= 75	12	15
Hypercholesterolemia:	Late effects BC study	CMR Nijmegen
Age in 2000:	%	%
< 45	0.2	0.4
45 – 64	12	7
65 – 74	17	16
>= 75	10	9

Abbreviations: BC, breast cancer; CMR, continuous morbidity registration.

Risk of CVA by RT field: Cox model analysis

Patients irradiated on the supraclavicular and/or IMC fields did not experience a higher risk of stroke or TIA compared with patients irradiated on fields other than supraclavicular or IMC fields or patients treated without RT (Table 5.5). Risk of stroke was most strongly associated with HT (HR = 1.88), hypertension (HR = 2.07), and hypercholesterolemia (HR = 1.64). For smoking and DM, we found nonsignificantly increased HRs of 1.37 and 1.33. In the analysis by primary treatment, where time at risk ended at date of treatment for recurrent disease, risk of stroke remained increased for adjuvant HT (HR = 2.14; 95% CI: 0.62 - 7.32; Table 5.5).

Discussion

This is the first long-term cohort study assessing the incidence of cerebrovascular events in early BC patients according to RT fields delivered. Overall, the risk of stroke was decreased by 25% in comparison with the general female population. Contrary to our expectation, risk of

Table 5.4. Overall risk of stroke and TIA, by age at start of treatment, treatment category and follow-up interval

	Stroke*					TIA				
	O	E	SIR	95% CI	AER#	O	E	SIR	95% CI	AER#
Overall	164	217.6	0.75	0.64 – 0.88	-15.2	109	133.3	0.82	0.67 – 0.99	-6.8
Age at start of treatment										
< 45 years	17	19.6	0.87	0.51 – 1.39	-2.3	12	6.80	1.76	0.91 – 3.08	4.5
45 – 54 years	52	56.9	0.91	0.68 – 1.20	-3.5	39	33.4	1.17	0.83 – 1.60	3.9
>= 55 years	95	141.0	0.67	0.55 – 0.82	-47.6	58	93.1	0.62	0.47 – 0.81	-35.9
			$P_{trend} = 0.1$					$P_{trend} < .0001$		
Treatment										
Surgery only	24	39.3	0.61	0.39 – 0.91	-31.0	11	24.6	0.45	0.22 – 0.80	-27.4
RT (± surgery)	90	134.4	0.67	0.54 – 0.82	-21.3	71	83.0	0.86	0.67 – 1.08	-5.7
RT+CT (± surgery)	10	10.7	0.94	0.45 – 1.72	-1.9	11	3.79	2.90	1.45 – 5.19	19.3
RT+HT (± surgery)	28	21.5	1.31	0.87 – 1.88	21.6	10	14.4	0.69	0.33 – 1.28	-14.5
RT+CT+HT (± surgery)	7	8.4	0.83	0.34 – 1.72	-6.0	4	5.2	0.77	0.21 – 1.97	-5.1
Follow-up interval										
10 – 14 years	51	84.8	0.60	0.45 – 0.79	-17.7	37	59.1	0.63	0.44 – 0.86	-11.5
15 – 19 years	70	75.6	0.93	0.72 – 1.17	-5.0	47	44.3	1.06	0.78 – 1.41	2.4
>= 20 years	43	57.2	0.75	0.54 – 1.01	-28.8	25	29.9	0.84	0.54 – 1.23	-9.9

Abbreviations: TIA, transient ischemic attack; O, observed number of events; E, expected number of events;
SIR, standardized incidence ratio; AER, absolute excess risk; RT, radiotherapy; CT, chemotherapy; HT, hormonal therapy.
* Type of stroke: 90% ischemic, 5% hemorrhagic, 5% unknown.
# Per 10,000 patients per year.

stroke was not increased in patients treated with adjuvant RT at the carotid arteries compared with non-irradiated patients. Of all treatment modalities, only HT was associated with an increased risk of stroke. Strongest risk factors were hypertension and hypercholesterolemia, but these factors did not modify the risk estimates for treatment.

Data on risk of stroke in BC patients are scarce. Recently, Jagsi et al. found a non-significantly elevated SIR of CVA (1.74; 95% CI: 0.94 - 2.37) in patients with early BC after a median follow-up of 6.8 years.[25] In the EBCTCG meta-analysis on effects of RT, the gain in BC survival from RT was partly offset by an increase of vascular mortality.[2] A recent update[3] showed that this excess vascular mortality mainly involved heart disease, whereas risk of stroke was not increased in irradiated versus non-irradiated patients. In a large population-based study (median follow-up, 5.4 years), Nilsson et al. found that BC patients had an overall relative risk (RR) of stroke of 1.12 (95% CI: 1.07 - 1.17) compared with the general population.[26] This increased risk was especially pronounced during the first year after diagnosis (RR = 1.22; 95% CI: 1.06 - 1.39). Possibly, the increase during the first year was caused by tumor-related coagulation disorders.[27,28] The effect of specific treatment regimens could not be examined because of lack of information. Retrospective studies of head and neck tumor patients and survivors of Hodgkin's lymphoma irradiated to the carotid region show a significantly increased risk

Table 5.5. Multivariate Cox regression analyses of potential risk factors for stroke and TIA

	Analysis based on total treatment		**Analysis based on primary treatment***
	Risk of stroke#	**Risk of TIA#**	**Risk of stroke#**
Risk Factor	HR (95% CI)	HR (95% CI)	HR (95% CI)
RT			
No RT/ fields not incl. carotid artery†	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
IMC only	1.04 (0.72 – 1.49)	1.39 (0.88 – 2.20)	1.00 (0.66 – 1.49)
Supraclavicular (± IMC)	1.04 (0.69 – 1.58)‡	1.45 (0.85 – 2.46)§	0.79 (0.47 – 1.33)
CT vs no CT	0.91 (0.53 – 1.57)	1.32 (0.71 – 2.47)	0.76 (0.33 – 1.76)
HT vs no HT	1.88 (1.28 – 2.75)	0.91 (0.52 – 1.59)	2.14 (0.62 – 7.32)
Smoking vs. never:			
Through the end of follow-up	1.37 (0.96 – 1.95)	1.33 (0.86 – 2.05)	1.24 (0.81 – 1.88)
Ex-smoker	1.00 (0.58 – 1.72)	0.74 (0.36 – 1.56)	0.89 (0.47 – 1.68)
Hypertension vs no/unknown	2.07 (1.49 – 2.87)	1.23 (0.81 – 1.86)	2.44 (1.65 – 3.60)
Diabetes Mellitus vs no/unknown	1.33 (0.88 – 2.00)	1.47 (0.86 – 2.49)	1.27 (0.78 – 2.05)
Hyperchol. vs no/unknown	1.64 (1.09 – 2.47)	1.69 (1.00 – 2.83)	1.89 (1.20 – 2.97)

Abbreviations: TIA, transient ischemic attack; HR, hazard ratio; RT, radiotherapy; IMC, internal mammary chain; CT, chemotherapy; HT, hormonal therapy.

* In the analysis based on primary treatment, time at risk ended at the date of treatment for recurrent disease.

Adjusted for age at diagnosis; furthermore, all listed variables were included in the model.

† Fields not including carotid artery: no IMC or supraclavicular field.

‡ Risk of stroke by laterality: HR for left supraclavicular field, 1.03 (0.61 – 1.71); for right supraclavicular field, 0.87 (0.49 – 1.54). In the analysis by laterality, time at risk would end at date of a contralateral BC, but only if the contralateral side had received RT. As a consequence, some events were excluded from the analysis and therefore the separate risk estimates for left- and right-sided tumors were somewhat lower than the risk estimate for RT in this region when laterality was not taken into account.

§ Risk of TIA by laterality: HR for left supraclavicular field, 2.00 (1.11 – 3.59); for right supraclavicular field, 0.84 (0.38 – 1.85).

of stroke. In BC patients, both left and right supraclavicular radiation portals include the ipsilateral CCA, with the left artery exposed over a slightly longer stretch than the right one. Therefore, we expected an increased risk of CVA, probably somewhat higher for RT on the left side. Overall, we found no increased risk of CVA. When analyzing by laterality, we observed an increased risk of TIA among women irradiated on the left supraclavicular region (HR = 2.00; Table 5.5, see footnote), whereas no such risk increase was found for the right side (HR = 0.84). No left-right difference was observed for stroke, however. Although there were some differences in fractionation schedules used in our study population, all schedules had a more or less equivalent biological effective dose. Consequently, we did not expect any differences in risk between these fractionation regimens.

HT such as tamoxifen increases the risk of venous thromboembolism, and some recently published studies have investigated risk of stroke associated with tamoxifen.[29-31] Results from a meta-analysis by Bushnell and Goldstein[8] showed an elevated risk of ischemic stroke (RR = 1.82; 95% CI: 1.41 - 2.36). However, the International Breast Cancer Intervention Study-I prevention study[29] and the nested case-control study by Geiger et al.[31]did not demonstrate a significantly increased risk of stroke with tamoxifen. In our study, we observed a nearly two-

fold elevated risk of stroke in patients treated with HT. However, tamoxifen is often prescribed for metastasized BC. Therefore, the association with tamoxifen may be confounded by the presence of active disease, which in itself may predispose to thrombosis[27] and thereby to ischemic stroke.[32] The separate effects of active disease and HT could not be disentangled in earlier studies.[29,31] Therefore, we assessed the influence of HT on the risk of stroke separately in patients without signs of relapse and again observed a (nonsignificantly) increased risk of stroke (HR = 2.14).

Our recent study on cause-specific mortality in BC patients already showed a (non-significant) 16% decrease in overall mortality from stroke.[20] Importantly, this study showed no mortality increase from stroke during the first 10 years of follow-up, justifying our decision to focus on 10-year survivors of BC in the current study. There are several explanations for reduced risk of stroke in long-term BC survivors compared with the general population. First, the risk profile for BC (e.g., late menopause) may be protective against (cerebro-)vascular disease.[33] In addition, women may opt for a healthier lifestyle (e.g., more exercise, healthier diet) after BC diagnosis, which would reduce their risk profile for stroke even more.[34,35] Although we did not observe a more favorable risk profile in the study population compared with the general population, our BC cohort may have been subject to more subtle changes in risk profile during follow-up (e.g., dietary changes, less smoking rather than cessation of smoking). Hypertension was even more frequently diagnosed in our BC population than in the general female population, probably as a result of surveillance bias. Paradoxically, this might explain the reduced risk of stroke. BC patients with known hypertension will receive treatment and thus reduce their risk of stroke, whereas a high proportion of the general population with hypertension may not be correctly diagnosed and thus will remain untreated. Finally, particularly in this cancer center-based study population, we may have studied BC patients with higher socioeconomic status, which has been reported to be associated with lower rates of vascular disease.[36,37]

Strengths of our study include the availability of data on all primary and follow-up treatments, including radiation fields, and on cerebrovascular risk factors. Follow-up was near complete and very long, with over 30% of patients followed for more than 20 years.

A potential weakness of our study concerns underreporting of CVA diagnoses. However, a study on cardiovascular risk in the same study population[38] rendered a significant 1.3–fold increased risk of cardiovascular disease, which was comparable to results from other studies.[2,5,39] In both studies on vascular events, we obtained information from GPs for the large majority of patients because a pilot study had shown that 20% of vascular events were not registered in oncologic records. Furthermore, since the GP was the source of information for both observed events and the reference rates used for comparison, any underreporting by GPs would not affect the validity of our results.

Although we had information on cardiac risk factors at baseline and also at follow-up, it was not always available at the time we were most interested in (i.e., at 10 years after first

treatment). We used hypertension, DM, and hypercholesterolemia as fixed covariates in the analysis with a positive score obtained at any point in time. Although this approach may have introduced some misclassification, this would be expected to bias our risk estimates to unity. As for smoking, this problem was largely avoided by using separate categories for smokers who continued smoking until end of follow-up and for ex-smokers (those who stopped at the time of BC diagnosis).

In conclusion, no association between stroke risk and irradiation to the supraclavicular nodes was found in our BC population. Although adjuvant HT[4] clearly improves BC survival, physicians should be aware of the increased risk of stroke after HT in long-term BC survivors.

Acknowledgment

We thank E.H. van de Lisdonk from CMR-Nijmegen for supplying us with incidence rates of cerebrovascular diagnoses; A.A.M. Hart (The Netherlands Cancer Institute, Amsterdam) for statistical advice; A.W. van den Belt-Dusebout, V.B. Hartog, S.E. Kraus, M.A. Kuenen, and the hospital cancer registries of the Netherlands Cancer Institute and the Erasmus MC, Daniel den Hoed Cancer Center for assistance in data collection. This study would not have been possible without the collaboration of more than 3500 physicians from throughout the Netherlands who provided follow-up data.

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6 Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume

Jacques H. Borger*, Maartje J. Hooning*, Liesbeth J. Boersma, Antonia Snijders-Keilholz, Berthe M.P. Aleman, Eelke Lintzen, Sara van Brussel, Peter-Paul van der Toorn, Maitham Alwhouhayb, Flora E. van Leeuwen

*Both authors contributed equally to this work.

Int J Radiat Oncol Biol Phys 2007; 69: 1131-8

Abstract

Purpose

To assess the risk of cardiovascular disease (CVD) after postlumpectomy irradiation restricted to tangential fields.

Methods and materials

We assessed the incidence of CVD in 1601 patients with T1-2N0 breast cancer (BC) treated with breast tangentials in five different hospitals between 1980 and 1993. Patients treated with radiation fields other than breast tangentials and those treated with adjuvant chemotherapy were excluded. For patients with left-sided BC, maximum heart distance (MHD) was measured on the simulator films as a proxy for irradiated heart volume. Risk of CVD by laterality and MHD categories was evaluated by Cox proportional hazards regression analysis.

Results

Follow-up was complete for 94% of the patients, and median follow-up was 16 years. The incidence of CVD overall was 14.1%, of ischemic heart disease 7.3%, and for other types of heart disease 9.2%, with a median time to event of 10 to 11 years. The incidence of CVD was 11.6% in patients with right-sided BC, compared with 16.0% in left-sided cases. The hazard ratio associated with left-sided versus right-sided BC was 1.38 (95% confidence interval [CI]: 1.05 - 1.81) for CVD overall, 1.35 (95% CI: 0.93 - 1.98) for ischemic heart disease, and 1.53 (95% CI: 1.09 - 2.15) for other heart disease, adjusted for age, diabetes and history of CVD. The risk of CVD did not significantly increase with increasing MHD.

Conclusions

Patients irradiated for left-sided BC with tangential fields have a higher incidence of CVD compared with those with right-sided cancer. However, the risk does not seem to increase with larger irradiated heart volumes.

Introduction

Increased cardiovascular mortality following radiotherapy (RT) for breast cancer (BC) was first noticed in Scandinavian and British trials.[1-4] This finding was later confirmed in meta-analyses of trials randomizing for postoperative RT[5-9] and in population-based studies using left/right comparisons.[10-15] These results concern mortality data in patients treated with either post-mastectomy or postlumpectomy irradiation, except for one study that exclusively examined postlumpectomy RT.[15] Few data are available regarding cardiac morbidity among patients treated with breast-conserving therapy.[16] In one modeling study a dose–volume effect was suggested.[17] The irradiated volume of the heart can be derived from measuring the maximum distance between the posterior field border and the heart contour in the beam's-eye view of a tangential treatment beam (Figure 6.1), also called the maximum heart distance (MHD),[18] enabling retrospective analysis of volume effects. To date no studies have been published that examined individual dose and volume effects in relation to the incidence of CVD.

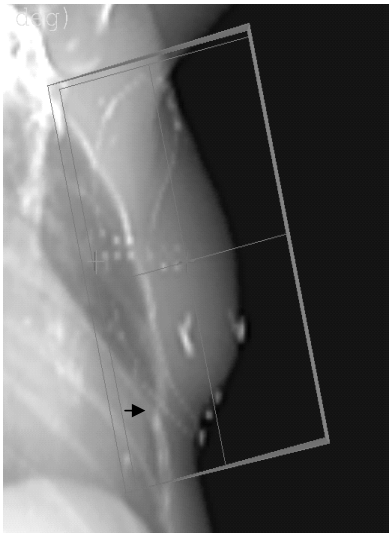

Figure 6.1. Simulator film showing measurement of maximum heart distance (MHD) from dorsal field border of tangential breast field (medio-lateral) to most distant heart contour (arrow).

In the present study we assessed the effect of tangential breast irradiation on CVD incidence by comparing left- and right-sided BC patients. Subsequently we evaluated whether increasing MHD was associated with greater risk of CVD in patients irradiated on the left side.

Methods and materials

Data collection

We included 1601 patients with stage T1-2N0 BC treated with breast-conserving therapy between 1980 and 1993 at five institutions: Catharina Ziekenhuis Eindhoven (n = 470), Eras-

mus MC/Daniel den Hoed Cancer Center (*n* = 399), MAASTRO Clinic (*n* = 340), Netherlands Cancer Institute (*n* = 199), and University Hospital Leuven (*n* = 193). Patients treated with radiation fields other than breast tangents and those treated with adjuvant chemotherapy were excluded, as were patients with bilateral BC or other secondary malignant tumors at the time of diagnosis of BC. From the oncologic records we collected the following data: date of BC diagnosis, laterality, tumour histology, axillary lymph node status, dates and treatment modalities of primary BC and of recurrent disease (type of surgery, radiation fields), history of cardiac disease before diagnosis of BC, dates of diagnoses of cardiac events, cardiovascular risk factors, date of most recent medical information or date of death, and primary cause of death according to the International Classification of Diseases, 9th edition. Radiotherapy information included number of fractions, total dose, beam energy, and boost irradiation. Risk factors (smoking, hypertension, hyper-cholesterolemia, and diabetes mellitus) were recorded both at the date of diagnosis of BC and at the end of follow-up. Smoking was scored positive when the patient was smoking at the end of follow-up or had stopped smoking less than 1 year before the end of follow-up. Hypertension, hypercholesterolemia and diabetes mellitus were scored as positive when stated in the medical information or when treated. For all patients we updated information until at least January 1, 2000 on specific cardiac diagnoses and risk factors, as well as vital status, by sending a questionnaire to their general practitioners (GP). In The Netherlands and in Belgium nearly all residents have a GP who receives all medical correspondence from attending physicians. Municipal registries were consulted for information on date of death when information was incomplete. For 81% of the patients we collected cardiac data from both the patient record and the GP and for the other 19% from the patient records only. Complete follow-up information until at least January 1, 2000 was available for 94% of the patients. For patients who died from an acute cardiac event, without prior evidence of cardiac disease, the date of death was recorded as date of diagnosis of the cardiac event.

Measurement of maximum heart distance

Three investigators (J.H.B., L.J.B., and E.L.) were trained to measure the maximum heart distance (MHD), and in a pilot study of 30 patients the level of agreement was established, resulting in the following policy. The MHD was measured independently by 2 investigators as the perpendicular distance from the dorsal field border to the most distant part of the heart contour visible on the simulator film (Figure 6.1). The results were averaged if less than a 3-mm interobserver difference was found. Cases with a larger disagreement were re-evaluated by the two observers until consensus was reached.

Treatment

Breast irradiation was given with tangentially opposing beams to a dose of 50 Gy in 25 fractions of 2 Gy in all patients, using megavoltage equipment (5-8 MV) in 89% of the cases.

Eleven percent of the patients was treated with ^{60}Cobalt machines. A boost was given in 96% of the patients.

Statistical analysis

Overall cumulative probabilities of death were estimated as a function of time since start of treatment using the Kaplan-Meier method.[19] The Cox proportional hazards model[20] was used to quantify the effects of laterality and MHD score on CVD risk, taking into account several covariates (age at treatment, cardiovascular risk factors). The Cox models were fitted with the use of SPSS statistical software (SPSS Inc, Chicago, IL). The chi-square test and Student's *t* test were used to compare categoric and continuous variables, respectively.

Results

For the 1601 patients included in the study, the median follow-up since start of RT was 16 years (range, 0.15 - 24.3 yrs). Median age at diagnosis of BC was 49 years (Table 6.1). Distribution of cardiac risk factors was not different for left- and right-sided BC patients, except for diabetes mellitus, which occurred more often in right-sided cases ($p = 0.02$), and history of CVD before BC diagnosis, which was reported more often in left-sided BC patients ($p = 0.07$, Table 6.1).

There was no significant difference in causes of death between the two groups (Table 6.2.). Overall and BC disease-free survival was not different for left- versus right-sided RT (Figure 6.2a and b). Comparison of overall cardiovascular mortality between patients treated on the

Table 6.1. Patient characteristics by breast cancer laterality

Characteristics	**right-sided BC**	%	**left-sided BC**	%	***P***
Number of patients	731	45.7	870	54.3	
Median age (years)	48.0		49.0		0.20
Median follow-up (years)	16.1		16.1		0.81
Risk factors for CVD					
Hypertension	157	21.5	208	23.9	0.26
Diabetes Mellitus	61	8.3	47	5.4	0.02
Hypercholesterolemia	111	15.2	118	13.6	0.39
Smoking:					
Never	281	38.4	324	37.2	0.64
Former smoker	64	8.8	95	10.9	
Current smoker	80	11.0	69	7.9	
Unknown	306	41.9	382	43.9	
CVD before BC diagnosis	7	1.0	19	2.2	0.07

Abbreviations: BC, breast cancer; CVD, cardiovascular disease.

Table 6.2. Causes of death

	Right-sided BC	%	Left-sided BC	%	*P*
All causes	172	23.5	214	24.6	0.64
Breast cancer	81	11.1	97	11.1	1.00
Other cancer	17	2.3	19	2.2	0.87
Cardiovascular disease	14	1.9	29	3.3	0.09
Myocardial infarction	5	0.7	14	1.6	0.11
Other heart disease*	9	1.2	15	1.7	0.54
Sudden death	5	0.7	5	0.6	1.00
Other causes	38	5.2	35	4.0	0.28
Unknown	17	2.3	29	3.4	0.23

Abbreviations: BC, breast cancer.

* International Classification of Diseases (9th edition) codes 420-429.

left side and on the right side rendered a hazard ratio (HR) of 1.57 (95% CI: 0.83 - 3.00; Figure 6.3), adjusted for age at BC diagnosis, history of CVD, and diabetes mellitus. Mortality from ischemic heart disease was nonsignificantly increased for left-sided RT, with a HR of 1.99 (95% CI: 0.71 - 5.59; data not shown).

Increased morbidity from CVD was statistically significantly associated with irradiation on the left side (HR = 1.38; 95% CI: 1.05 - 1.81), adjusted for age at diagnosis of BC, history of CVD and diabetes mellitus (Table 6.3, Figure 6.4). The median time to event was 10.5 years. The increase of CVD incidence was observed not only in the category of ischemic heart dis-

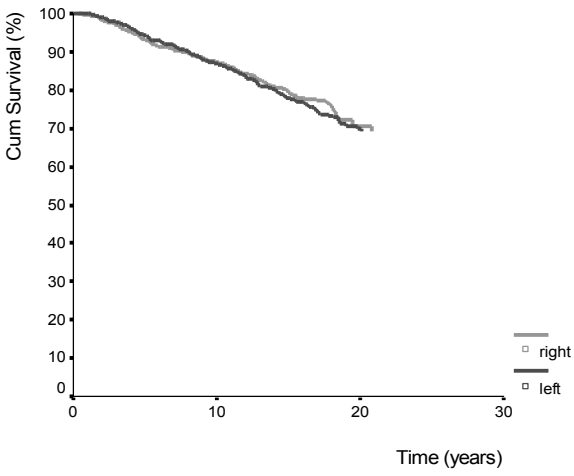

Figure 6.2a. Overall survival by laterality
HR left vs right: 1.05 (95% CI: 0.86 – 1.28)

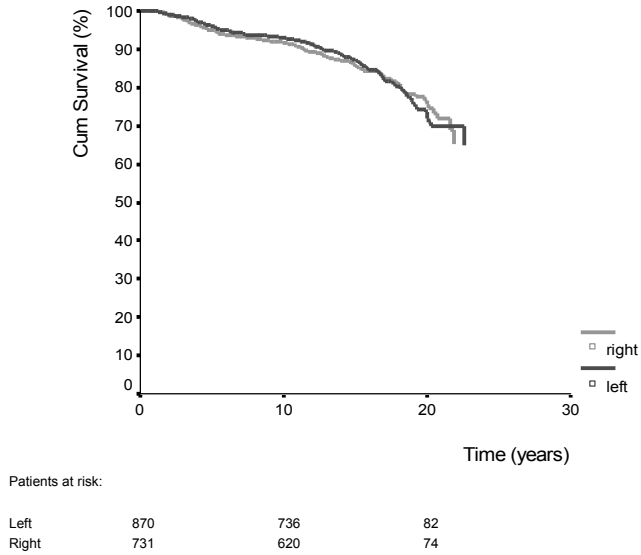

Figure 6.2b. Survival from breast cancer by laterality
HR left vs right: 1.00 (95% CI: 0.79 – 1.27)

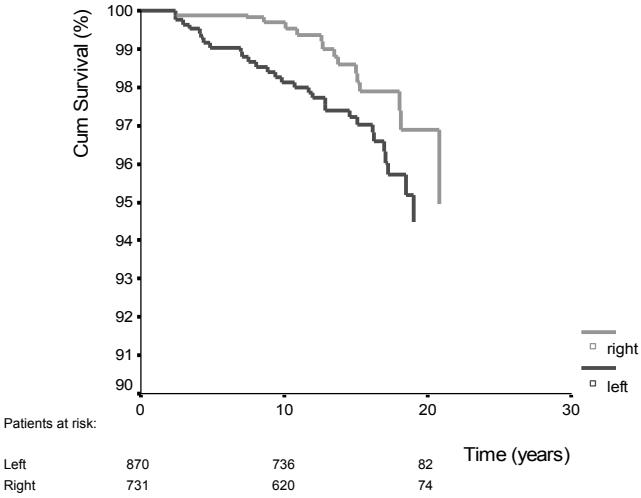

Figure 6.3. Survival from CVD by laterality; Cox regression analysis, adjusted for age at BC diagnosis, history of CVD and DM.
Abbreviations: BC, breast cancer; HR, hazard ratio; CVD, cardiovascular disease; DM, diabetes mellitus.
HR left vs right: 1.57 (95% CI: 0.83 – 3.00)

ease, with a marginally significantly increased risk of 1.35 (95% CI: 0.93 - 1.98), but also in the category of other heart diseases (HR = 1.53; 95% CI: 1.09 - 2.15), consisting of pericarditis, valvular dysfunction, cardiomyopathy, dysrhythmias and congestive heart failure. There was no statistically significant difference in the risk of cardiovascular disease between patients

Table 6.3. Cardiovascular morbidity by laterality* (Cox regression analysis)

	Right-sided BC ($n = 731$)	%	Left-sided BC ($n = 870$)	%	HR (95% CI)
All cardiovascular disease	85	11.6	139	16.0	1.38 (1.05-1.81)
Ischemic heart disease†	44	6.0	73	8.4	1.35 (0.93-1.98)
Other heart disease‡	53	7.3	94	10.8	1.53 (1.09-2.15)

Abbreviations: BC, breast cancer; HR, hazard ratio; CI, confidence interval.

* Adjusted for age at BC diagnosis, history of CVD and DM.

† International Classification of Diseases (9th edition) codes 410-414.

‡ International Classification of Diseases (9th edition) codes codes 420-429.

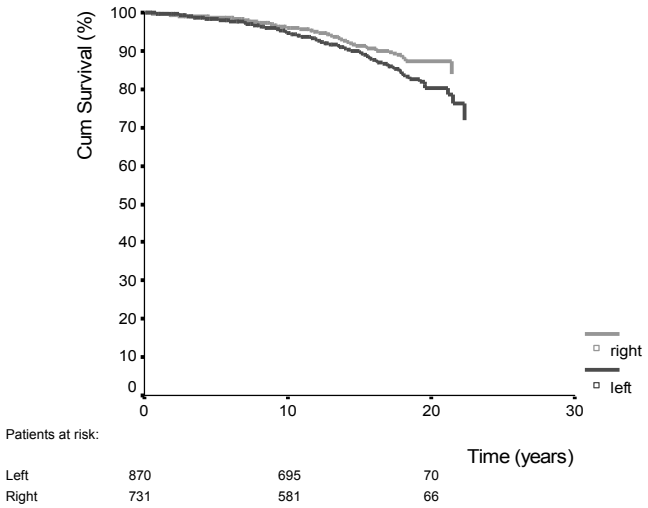

Figure 6.4. Survival free of cardiovascular disease by laterality, adjusted for age at BC diagnosis, history of CVD and DM.
Abbreviations: BC, breast cancer; HR, hazard ratio; CVD, cardiovascular disease; DM, diabetes mellitus.
HR left vs right: 1.38 (95% CI: 1.05 – 1.81)

irradiated with ^{60}Co beams and those treated on linear accelerators. Apart from left-sided irradiation, other independent risk factors for increased cardiovascular morbidity were previously diagnosed CVD, high blood pressure, hypercholesterolemia, and diabetes mellitus; risk from continued smoking was marginally significantly increased (Table 6.4). Exclusion of the patients with a history of CVD from the analysis rendered similar results with respect to risk of CVD from RT (HR for left- vs right-sided RT = 1.42; 95% CI: 1.08 - 1.87).

Simulator films needed for MHD measurement were missing in 74 patients with left-sided BC. Maximum heart distance was measured in 796 patients with left-sided BC and not evaluable in 18 cases. Disagreement (> 3 mm difference) between the two observers occurred in 154 cases. Concordance was eventually reached in all cases. Mean MHD was 13.4 mm, with a range of 0 - 48 mm.

When examining the effect of MHD (as a proxy measure of irradiated heart volume) on CVD risk, no significant trend of increased risk with greater MHD could be observed (Table 6.5). Patients with MHD > 30 mm seemed to have a higher risk of ischemic heart disease as com-

Table 6.4. Cox regression analysis of potential risk factors for CVD

Variable	HR* (95% CI)
Radiotherapy left vs right	1.33 (1.01-1.74)
Hypertension yes vs no	1.39 (1.04-1.85)
Diabetes mellitus yes vs no	1.96 (1.35-2.86)
Hypercholesterolemia yes vs no	1.74 (1.26-2.40)
Smoking:	
current vs never	1.51 (0.96-2.39)
stopped vs never	1.39 (0.87-2.22)
unknown vs never	0.92 (0.68-1.24)
History of CVD yes vs no	2.32 (1.46-3.70)

Abbreviations:HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

* Adjusted for age, hypertension, DM, hypercholesterolemia, smoking and history of CVD.

Table 6.5. Cardiovascular morbidity* by MHD measurements (Cox regression analysis)

		Ischemic heart disease		Other heart disease		All cardiovascular disease	
MHD	**Patients (*n*)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**	**Events**	**HR (95% CI)**
Right	731	44	1.00	53	1.00	85	1.00
Left	778	73†		94‡		139§	
0 mm	98	5	1.07 (0.42-2.71)	11	2.14 (1.14-4.04)	14	1.63 (0.94-2.84)
0-10 mm	187	15	1.51 (0.84-2.73)	19	1.60 (0.94-2.72)	29	1.48 (0.97-2.28)
10-20 mm	325	29	1.36 (0.85-2.19)	31	1.15 (0.74-1.81)	51	1.21 (0.85-1.71)
20-30 mm	140	9	1.03 (0.50-2.13)	9	0.77 (0.38-1.56)	15	0.81 (0.47-1.41)
>30 mm	28	4	1.88 (0.67-5.30)	6	2.18 (0.92-5.14)	8	1.73 (0.83-3.62)

Abbreviations: MHD, maximum heart distance; HR, hazard ratio; CI, confidence interval.

* Adjusted for age, history of cardiovascular disease and diabetes mellitus.

† 11 events of ischemic heart disease in patients with missing MHD measurement.

‡ 18 events of other heart disease in patients with missing MHD measurement.

§ 22 events of cardiovascular disease in patients with missing MHD measurement.

pared with patients with smaller MHD measurements, although the numbers were too small to reach statistical significance.

Discussion

In this large, multicenter study we focused exclusively on patients treated for postlumpectomy RT with breast tangentials only and observed an increased incidence of CVD for left-sided BC compared with right-sided BC, irrespective of the volume of the heart in the radiation field. With respect to mortality from CVD, left- versus right-sided RT showed a statistically nonsignificant increased risk of similar magnitude. Cardiotoxic effects resulting from RT have been known since publications on late side effects of treatment in patients with

Hodgkin's lymphoma.[21-24] Many cardiac disorders have been described as a result of irradiation: coronary artery disease, valvular insufficiencies, pericarditis and cardiomyopathies. The basic feature of this particular tissue damage in the heart is fibrosis occurring in a dose- and volume-dependent way.[25]

Cardiovascular mortality: comparisons between irradiated and non-irradiated patients

The first indications of a possible negative effect from irradiation in the treatment of BC were seen in the Oslo and Stockholm trials randomizing for postmastectomy irradiation.[1,2] A clear excess mortality from myocardial infarction (MI) was noticed in the irradiated group. A cardiotoxic effect due to various cardiac diseases was also found in two British trials.[3,4] The first meta-analysis of eight postmastectomy trials showed an increased all-cause mortality of approximately 30% in the irradiated group, whereas in an updated report the excess mortality seemed to be confined to heart disease (relative risk [RR] = 1.62 for irradiated vs non-irradiated patients).[5,6] The overviews of the Early Breast Cancer Trialists' Collaborative Group also reported increased cardiovascular mortality in the irradiated group (RR = 1.27).[7-9] In their latest publication, the absolute reduction in BC mortality was 5% after 15 years of follow up, against an absolute increase in non-BC mortality of 1%, resulting in a net positive effect from adjuvant RT.[9] In the Dutch late effects BC study, excess cardiovascular mortality resulting from RT was found in the postmastectomy population (RR =1.5). In patients treated with postlumpectomy RT, cardiovascular mortality was not elevated, suggesting more favorable results from improved RT techniques.[13]

Left-right comparisons with respect to cardiovascular mortality

Left–right comparisons have been made in several studies to estimate cardiac mortality caused by irradiation; most studies concerned mixed populations of patients treated with postmastectomy and postlumpectomy RT. In a population-based study of the Surveillance Epidemiology and End Result (SEER) registries, the cardiovascular mortality ratios for patients with left-sided irradiation vs. those irradiated on the right side were 1.37 and 1.53 at 10 and 15 years of follow-up, respectively.[12] However, for patients treated with breast conservation in this cohort, the follow-up in the second decade after treatment was too limited to allow firm conclusions regarding the postlumpectomy group.[10-12] In addition, radiation treatment regimens included different target volumes in the time periods studied. Furthermore, no information was available on how many patients were also treated with internal mammary fields; radiation of the internal mammary nodes, not only on the left but even on the right side, may cause considerable radiation doses to the heart. Another cause-specific mortality analysis by laterality was performed in the Swedish Cancer Registry, showing excess MI mortality in 10-year survivors (30% irradiated) with BC on the left side (RR = 1.13).[14] In one study of patients from the Ontario Cancer Registry, exclusively postlumpectomy irradiation was analyzed. A higher risk of mortality from MI was observed in irradiated patients with left-

sided BC (RR = 2.10), adjusted for age at BC diagnosis.[15]The absolute excess cardiac mortality due to irradiation in BC treatment is estimated to be as small as 1% to 2%, which renders many studies underpowered in this regard. With such small differences it is not surprising that several studies come to opposite conclusions: no excess cardiovascular mortality from RT.[26-28]

Cardiovascular morbidity after RT for BC

Only few studies have presented data on the incidence of cardiovascular events. By studying cardiovascular morbidity the number of events will be larger, enabling statistically more powerful analysis. Indeed, although we did not find a significant left-right difference for CVD mortality, the difference for CVD morbidity was significant. This corresponds to the recent findings by Harris et al.[16], who made a left-right comparison in 961 patients treated with post-lumpectomy RT and found no excess cardiac mortality in patients treated on the left side. However, the incidence of coronary artery disease was increased for patients with left-sided BC. At 20 years the survival free of MI was 95% versus 85% for patients treated for right- and left-sided BC, respectively. In this study 26% of the patients had additional radiation fields (14% internal mammary fields) and 33% had chemotherapy (7% adjuvant doxorubicin).[16] Two other studies recently reported data on CVD incidence after RT for BC. Patt et al.[29] evaluated risk of ischemic heart disease, valvular heart disease, congestive heart failure, and conduction abnormalities and found no statistically significant differences in cardiac morbidity after radiation among patients who were treated from 1986 to 1993. Mean follow-up was only 9.5 years, however. The Dutch late effects BC study,[30] on the other hand, with a median follow-up of almost 18 years, reported increased risks of myocardial infarction, valvular dysfunction, and congestive heart failure after RT administered after 1980. Breast irradiation only was not associated with increased risk of cardiovascular disease, but the number of patients in this study treated with breast tangentials (n = 688) was probably too small to detect a potential difference in risk.

Volume effects for risk of CVD

Gagliardi et al. developed a normal tissue complication probability model for fatal MI based on the data from patients treated in the early Stockholm trials.[17] In this model a clear volume effect was seen with three-dimensional analysis (CT scan). However, the model was based on a limited number of patients treated with relatively old radiation techniques.[17] It has been assumed that the irradiated heart volume can be estimated by measuring the MHD in the irradiation beams, as shown by Hurkmans et al.[18] However, no dose–volume relationship for heart disease could be established by MHD measurement in this study. Maximum heart distance may not be such a good indicator for actually irradiated heart volume after all, since organ motion plays a role. Simulator films are snapshots, and more accurate information could come from actual treatment films (megavoltage imaging). Some megavoltage imaging

data suggest that the MHD is somewhat overestimated by simulator films.[31] However, our data seem to exclude large differences between the MHD categories and do not support the hypothesis of a dose–volume effect at this dose level (25-50 Gy).

Strengths and limitations of the study

As far as we know, this is the largest study on risk of CVD in patients treated with breast tangentials only. Treatment with adjuvant chemotherapy, which may act as an independent risk factor for CVD, was excluded. We also had information on radiation regimens administered during follow-up; time-at-risk ended if other radiation fields were treated in case of local recurrence or contralateral BC. Unlike most studies, we approached GPs actively and collected information not only for ischemic heart disease but also for other types of heart disease, as well as for cardiac risk factors. Follow-up was nearly complete and potentially long enough to detect differences in CVD risk between left- and right-sided irradiation. Analysis by laterality has the advantage of the least possible chance to introduce bias. Indeed, the distribution of patient characteristics between left- and right-sided treated patients was very similar for all cardiac risk factors, except for diabetes mellitus and previously diagnosed CVD. These were considered chance findings and were adjusted for in the Cox regression analyses.

Unfortunately, for a considerable number of left-sided irradiations (n = 74) the MHD could not be measured because the simulator films were missing. However, the patient characteristics of this group were not different from the others, and conclusions concerning increased cardiovascular morbidity associated with left irradiation remained the same when left-sided cases without MHD measurements were excluded.

A boost was given in 96% of the cases in this study population. Exact information in terms of cardiac dose from the boost cannot be obtained in retrospect. However, in two institutions the boost was given with iridium implants and in one institution with implants and electrons. Photon boosts were used in only two institutions in some patients. Detailed information on cardiac volumes irradiated to a high dose with photon boosts is missing, but the number of patients is probably low. It is estimated that in the majority of the patients the boost only moderately contributed to the total heart dose (approximately 0.6 -2.5 Gy). Because a boost was given in almost all cases, we do not consider it as a confounding factor.

Our finding that even with an MHD of 0 mm more cardiotoxic effects occurred compared with right-sided RT may indicate that lower doses are relevant. In the MHD=0 category the irradiated heart volume exposed to doses lower than 50% of the prescribed dose (< 25 Gy) may be considerable. Unfortunately, we do not have data on the clearance value between the heart contour and the field border (negative MHD) to look for volume effects at lower dose levels. Some data suggest cardiac side-effects resulting from low-dose radiation.[32-36] Our findings may point in this direction but need to be confirmed. Alternatively, the relevant exposure parameter could also be radiation dose to the left anterior descending coronary artery, warranting further research.

Lack of knowledge about radiation parameters determining the excess CVD risk is related to the fact that the nature of heart damage after RT is poorly understood. Coronary artery disease seemed to be the obvious explanation,[37] but how do we explain the increased risk for other types of heart disease, as observed in our and other data? According to prospective single photon emissioncomputed tomography studies in patients treated for BC, tangential beams induce persisting localized myocardial perfusion defects compatible with transmural microvascular damage and resulting in wall motion disturbances.[38] This may explain why the spectrum of heart diseases after irradiation found in our study and in many others is not limited to coronary artery disease.

Conclusions

Nowadays many patients are treated with breast-conserving therapy for low-risk invasive BC and very often for ductal carcinoma in situ. Increased risk of CVD after left-sided postlumpectomy RT with breast tangentials, if confirmed by others, should be carefully weighed against the benefits of adjuvant RT.[9]

Modern RT has sophisticated techniques at its disposal to treat target volumes more precisely and to spare normal tissues more effectively.[39-42] Further study is needed to establish the dose levels below which no measurable cardiotoxic side effects occur. Meanwhile, we suggest the application of heart-sparing techniques in the radiotherapeutic treatment of BC.

Acknowledgment

The authors wish to express their gratitude to the datamanagers: G. Besseling, M. Kuenen, G. Ouwens, A. de Mol - van der Velde, S. Loffeld.

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7 Discussion

This thesis evaluates the long-term adverse effects of treatment for breast cancer. The need for this type of study may be attributed in the first place to the prolonged life expectancy of those treated. The risk increases discussed in this thesis are moderate, both for second cancers and cardiovascular disease. Yet, because of the high and increasing prevalence of breast cancer, with nearly 12,000 new patients in the Netherlands in 2006[1], these modest risks may cause increasing numbers of excess cases of cardiovascular disease and second malignancies in the Dutch population of breast cancer survivors, and will affect not only the net mortality but also long-term quality of life.

This chapter is not meant to repeat the contents of the discussions given in the previous chapters, to which we may refer directly. The aim of this section rather is to discuss some additional issues of interest related to the design and results of the Late Effects Breast Cancer (BC) Study.

Topics for discussion are:

- Active follow-up
- New findings in perspective
- Mechanisms underlying cardiotoxicity of radiotherapy and chemotherapy
- Contradictory results
- Limitations of presented studies on late adverse effects
- Clinical implications
- Recommendations for further research

Active follow-up

When studying rare events completeness and quality of follow-up data are very important. With incomplete follow-up, overestimation of risk for the event of interest occurs when follow-up in the original treatment center is more complete for survivors who develop the event of interest than for those who remain healthy. This is likely to happen when studying second cancer risk, because patients who remain healthy tend to lose contact with the medical system, whereas patients with a second cancer seek clinical follow-up.[2] In case of studying cardiac risk, however, underestimation is more likely to occur because patients with cardiovascular disease may seek medical care outside the original cancer treatment center. For this reason we made quite an effort to collect the most recent follow-up data for every patient.

Many studies on late side effects perform linkage of patients with death-certificate registries in case of mortality as the study-outcome of interest[3-5], or with hospital discharge registries when incidence of disease is studied.[6] When using hospital registries, all events diagnosed outside the hospital will obviously be lost. The simplest solution, extracting information from the patients' record of the cancer clinic, is an option when studying second malignancies, on

the condition that follow-up is complete. In case of non-cancer events, however, we cannot rely on the completeness of data in an oncologic record, as we showed in a pilot study on 377 patients. We compared the information on cardiovascular events obtained from general practitioners (GPs) with information from the oncologic records and found that 20% of all events were not registered in the patients' record. Particularly ischemic heart disease, heart failure and dysrhythmias were reported more often by the GPs. Therefore we opted for a so-called active follow-up approach, and sent questionnaires to all GPs of patients lost to follow-up (n = 2965), in order to complete the information on the medical status and treatment of breast cancer. In addition, we approached GPs of all 10-year survivors to collect information on cardiovascular disease and risk factors for cardiovascular disease. This was a very labor-intensive job because many patients as well as many GPs had moved since the last medical contact with the clinic. Therefore, in the course of the study we developed a searching strategy for GPs (Figure 7.1):

First we sent a letter to the GP last known from the medical record. In case of no response, we contacted the municipal registry of the council the patient was registered with and obtained up-to-date information on vital status and address of the patient. If the patient was still alive and resided at the last known address, we sent another letter to the GP– if necessary followed by a phone call. If the patient had died 10 years or less before the date of our enquiry, we sent a second letter to her GP, with a clear note of the date of death in case her medical file should be looked for in another archive. If the patient had moved we tried to find her new GP through pharmacies in the neighborhood or simply by postal code. However, if it turned out that the patient had died more than 10 years before, we experienced that it was not efficient to continue follow-up efforts because the relevant medical information was not traceable anymore - most likely being destroyed. Here we are faced with the consequences of a privacy law in medicine adopted in 1995 (WGBO, Wet Geneeskundige Behandelings Overeenkomst)

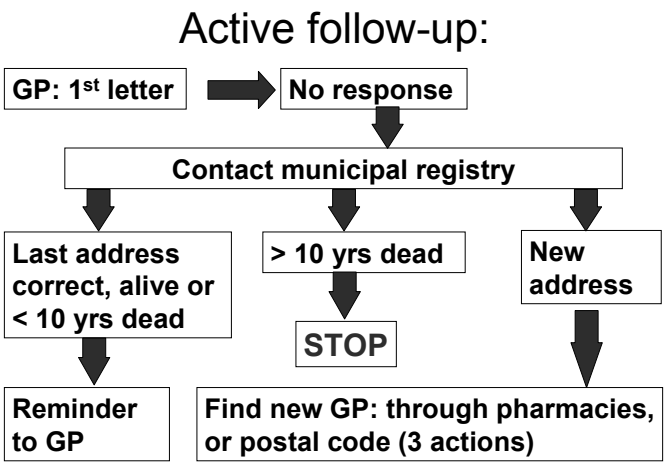

Figure 7.1. Flow chart for approach of GPs

which allows physicians to destroy medical records of patients who have not visited the clinic/practice for more than 10 years.[7] Initially this law implied that after the transition period had passed (2005), it would be even unlawful to keep old records for more than 10 years if there was no clinical necessity to do so, to protect the patient's privacy. Consequently, evaluation of late effects of many medical treatments would no longer be possible in the Netherlands. For this reason a committee of the Health Council of the Netherlands has now recommended a change in the law. A proposal has been made for a longer retention period for the care of the patient, a statutory regulation governing retention for research purposes and supplementary provisions that make it possible to retain hereditary data in the interest of relatives.[8,9] In the meantime, however, many patient data have already been destroyed after 10 years. Medical professional groups and patients' associations should exert their influence on the decision process in government, and stress the seriousness of the situation in order to prevent further destruction of medical data.

Despite these setbacks we succeeded to collect follow-up data for 83% of all 10-year survivors from their attending GPs. For the remaining 17% we collected data from the oncologic records only. Complete follow-up information through at least January 1, 2000, was available for 96% of all 10-year survivors.

New findings in perspective

Active completion of follow-up made our study an ambitious one. When putting so much effort into a study, we should ask the question: what additional information has this study brought which could not have been accomplished by linking registries?

We had detailed treatment information, on treatment regimens, individual radiotherapy fields and measurements of maximum heart distance (MHD), and, very importantly, also on dates and regimens for recurrent disease; we had information on classic cardiovascular risk factors, family history of breast cancer, and on various outcomes, both mortality and incidence, of malignant disease and a wide range of cardiac diagnoses.

The added value of this information is reflected in many of the new findings of our studies:

With respect to breast cancer mortality:

- After 25 years of follow-up, breast cancer mortality was still 6-fold increased compared with the general population (chapter 2); even in the selection of all long-term survivors who had no evidence of disease after 15 years, BC mortality was still 4.8-fold increased (Table 7.1).

With respect to the risk of contralateral breast cancer (CBC):

- Among patients treated before age 45 we found a significant dose-response relationship of radiotherapy with the risk of medially located CBC (chapter 3);

Table 7.1. Mortality from breast cancer in 15-year disease-free survivors ($n = 3006$)

	Breast cancer death				
	O	**E**	**SMR**	**95% CI**	**AER***
Overall	101	20.9	4.83	3.94 – 5.87	49.8
Age at diagnosis					
< 45 years	28	4.16	6.72	4.47 – 9.73	46.5
45 – 55 years	44	7.85	5.60	4.07 – 7.53	54.8
≥ 55 years	29	8.90	3.26	2.18 – 4.68	46.1

Abbreviations: O, observed number of deaths; E, expected number of deaths; SMR, standardized mortality ratio; AER, absolute excess risk *per 10,000 patient-years.

- Postlumpectomy radiotherapy as administered in the 1980s was associated with increased risk of CBC (chapter 3);
- The risk increase was even more pronounced in young patients with a positive family history for breast cancer (chapter 3);
- Continued smoking appeared to be an independent risk factor for CBC (chapter 3).

With respect to the risk of cardiovascular disease:

- Radiotherapy to the internal mammary chain (IMC), regardless of laterality, was associated with an increased risk of cardiovascular disease (both myocardial infarction and congestive heart failure, chapter 4);
- For patients irradiated after 1980, the risk of myocardial infarction was not increased anymore, while risks of congestive heart failure and valvular dysfunction remained increased for radiotherapy to the IMC - particularly when combined with breast or chest wall field (chapter 4);
- In general, the risk of cardiovascular disease increased with increasing mean cardiac dose (except for the risk of myocardial infarction for patients treated in 1980 – 1986, chapter 4);
- The effect of radiotherapy on cardiovascular disease was stronger among smokers than non-smokers (chapter 4);
- Treatment with radiotherapy plus chemotherapy (cyclophosphamide, methotrexate and fluorouracil) was associated with a higher risk of congestive heart failure than treatment with radiotherapy alone (chapter 4);
- Among patients treated with breast tangentials only we found an increased risk of cardiovascular disease when comparing left-sided with right-sided radiotherapy (chapter 6);
- A trend of increasing cardiac risk with increasing MHD could not be established (chapter 6);
- Even in case of MHD = 0 mm, the risk of cardiovascular disease appeared to be increased (chapter 6);

With respect to the risk of stroke:

- Patients irradiated on the supraclavicular area did not experience a higher risk of stroke compared with patients who were not irradiated on fields including the carotid artery (chapter 5);
- The effect of hormonal treatment with tamoxifen on risk of stroke was established separately from the thrombo-embolic effect of active disease (chapter 5).

With respect to second malignancy risk we focused on the incidence of contralateral breast cancer, although we found increased risks for some other cancers as well, as listed in Table 7.2.

Interestingly, the incidence ratios of both lung and esophageal cancer increased over time, p_{trend} = 0.10, a pattern to be expected in case of radiation-related risks. For leukemia, risk

Table 7.2. Risk of second malignancies: incidence overall, and by follow-up interval (lung cancer, esophageal cancer, leukemia) in the Late Effects BC Study (n = 7425)

	O	E	SIR	95% CI	AER*
Overall	994	623.0	1.60	1.50 – 1.70	46.0
contralateral breast	503	173.0	2.91	2.66 – 3.18	46.1
lung	76	34.2	2.22	1.75 – 2.78	5.2
esophagus	16	4.7	3.40	1.95 – 5.53	1.4
connective tissue	14	3.2	4.33	2.39 – 7.34	1.3
melanoma	32	14.8	2.16	1.48 – 3.05	2.1
ovary	49	31.4	1.56	1.15 – 2.06	2.2
AML	10	3.7	2.70	1.30 – 4.97	0.8
Follow-up interval: lung					
1 – 5 years	8	4.9	1.63	0.71 – 3.22	1.2
5 – 15 years	37	17.4	2.13	1.50 – 2.93	4.8
>= 15 years	31	10.8	2.87	1.95 – 4.07	14.1
			$P_{trend} = 0.10$		
Follow-up interval: esophagus					
1 – 5 years	1	0.5	2.08	0.05 – 11.6	0.2
5 – 15 years	5	2.3	2.20	0.72 – 5.14	0.7
>= 15 years	10	1.9	5.38	2.58 – 9.89	5.6
			$P_{trend} = 0.10$		
Follow-up interval: leukemia					
1 –5 years	4	0.7	5.71	1.56 – 14.6	1.3
5 – 15 years	4	1.8	2.25	0.61 – 5.75	0.5
>= 15 years	2	1.1	1.91	0.23 – 6.88	0.6
			$P_{trend} = 0.16$		

Abbreviations: AML, acute myeloid leukemia; O, observed number of events; E, expected number of events; SIR, standardized incidence ratio; AER, absolute excess risk *per 10,000 patient-years.

increase was present early during follow-up, particularly during the first five years, and disappeared afterwards. It is also clear from the literature that chemotherapy-induced leukemia has a much shorter induction period than radiation-induced solid malignancy. Unlike studies of Hodgkin lymphoma survivors, which reported increased risks of solid tumors from chemotherapy[10-12], we did not find any indication for increased solid tumor risk associated with chemotherapy for breast cancer, not even after more than 15 years of follow-up.
Late effects of hormonal treatment (HT) for breast cancer with tamoxifen have not been discussed elaborately in this thesis. Indeed, we found increased risk of stroke following HT, as was reported by others before.[13,14] The number of patients receiving HT in the adjuvant setting however, was quite small (n = 104; 2.4% of all 10-year survivors) and hampered further stratified analysis.

Mechanisms underlying cardiotoxicity of radiotherapy and chemotherapy

The pathogenesis of radiation-induced heart disease has been studied extensively over the past two decades, both in experimental and clinical studies.[15-18] The critical target structure appears to be the endothelial lining of blood vessels, in particular small arteries. According to the latest insights vascular damage may lead to tissue hypoxia, and, after many years, to a slowly progressive fibrogenesis of the myocardium.
We still do not know exactly what the relevant outcome is in studies on radiation-associated cardiac risk. Until recently cardiac risk was believed to be restricted to ischemic heart disease; now a growing body of evidence, including our study, is reporting on increased risks for other types of heart disease as well.
Furthermore, we also lack insight into the relevant radiation exposure to the cardiovascular system, and several options have been considered:

- mean radiation dose to the heart;
- dose-volume to the heart;
- maximum radiation dose to (a substantial part of) the heart;
- radiation dose to critical structures like the coronary arteries.

In our studies we used two different exposure measures: mean radiation dose to the heart (chapter 4), and maximum heart distance as a proxy for irradiated heart volume (chapter 6). However, these may well be not the most relevant exposures needed for evaluating radiation-induced cardiac disease.
Clearly some important questions still need to be answered:

- Which part of the heart is the most radiosensitive and should be chosen as a reference point for tolerance doses?
- Is there a threshold dose below which the risk is not increased?
- Is there a dose-volume relationship for the risk of cardiovascular disease?

- Is the clinical course of cardiovascular disease induced by radiation doses the same as that of cardiovascular disease developing in the absence of radiotherapy?

Likely, radiation to different structures of the heart may lead to different cardiac symptoms, e.g., radiation of the left anterior descending (LAD) coronary artery may lead to ischemic heart disease while radiation of the capillary network of the myocardium may lead to myocardial degeneration and heart failure. Imaging techniques may help here in depicting the exact structures damaged by radiation.

Several small studies investigated vascular abnormalities and cardiac function in asymptomatic patients during the first few years after radiotherapy.[19-23] Although cardiac damage is not expected to emerge until 10 years after radiation, the initiation of damage must have taken place at the time of the radiotherapy, which explains the interest in early changes. Vascular damage can be assessed by myocardial perfusion scintigraphy, a specific technique for the detection of cardiac perfusion abnormalities. A perfusion defect may result from obstruction of a coronary artery or from microvascular damage to the myocardium. In general, the incidence of perfusion defects is strongly correlated with the volume of left ventricle in the radiotherapy field. These perfusion defects occur in approximately 40% of patients within 2 years of radiotherapy for left-sided breast cancer, and are associated with corresponding wall-motion abnormalities. However, the clinical importance of these defects is uncertain. Additional prospective follow-up of a larger number of patients is needed to better define the long-term functional consequences of radiation-induced perfusion defects.

We reported on late heart failure due to CMF-chemotherapy in combination with radiotherapy; in breast cancer studies this has not been observed before, but probably the follow-up time in other studies was too short. Our data even suggested a modifying effect of radiotherapy on chemotherapy-related risk, although we were not able to confirm this because of lack of data on patients treated with chemotherapy only. Although it may be a spurious finding, this should be evaluated in other large studies with data on both radiotherapy and chemotherapy regimens. We can only speculate on the mechanism involved. Short-term toxicities of cyclophosphamide and fluorouracil have been described; however, this concerned reversible cardiac symptoms.[15]

Contradictory results

Some results from the various studies presented in this thesis seem to be inconsistent with each other and need to be discussed. Based on results from the Late Effects BC cohort, we reported that breast irradiation only was not associated with increased risk of CVD (chapter 4). The number of patients in this study treated with breast tangentials was relatively small (n = 688), with only few cardiac events, and after extension of the study population with patients from three other Institutions for the MHD study (n = 1601) we found moderately but

significantly increased risk estimates for left- versus right-sided breast irradiation (chapter 6). Despite the long median follow-up of 16 years, the number of 688 patients apparently was too small to detect a potential difference in risk.

Increased incidence of stroke was associated with hormonal treatment, both overall and when restricted to primary treatment, while there was no mortality from stroke among the patients treated with HT in the adjuvant setting only. Apparently some patients who received HT only as primary treatment developed a stroke, but none of them died from it.

Chemotherapy use (CMF) in the 1980s was associated with an increased risk of congestive heart failure, while among patients treated between 1970 and 1980 no such association was found for chemotherapy. When we restricted the analysis to primary treatment (1970-1980) in patients who had no recurrent disease, risk of heart failure was increased, however, although not significantly (HR = 1.85; 95% CI: 0.90 - 3.81). The number of patients who received adjuvant CMF in this period was small (n = 82).

We also considered residual confounding as a possible explanation for the chemotherapy effect, because all patients who received chemotherapy were treated with radiation as well. This could occur especially when patients treated with radiotherapy plus chemotherapy received more often radiation to the IMC than patients who were treated with radiotherapy only. However, when we analyzed the effect of chemotherapy specifically in all patients irradiated to the IMC, risk of congestive heart failure was still increased for treatment with chemotherapy: HR = 1.6 (95% CI: 1.1 - 2.3) for chemotherapy plus radiotherapy to the IMC vs radiotherapy to the IMC only.

Limitations of presented studies on late adverse effects

We should realize that the need for a study on late effects has arisen by virtue of success of cancer therapy. It would be informative to express the therapeutic benefits against the adverse effects in terms of survival for a direct evaluation of treatment benefit. For that purpose, however, a randomized clinical trial is needed, with a well-balanced distribution of adjuvant treatments over categories of age and stage at breast cancer diagnosis. Observational studies as conducted in this thesis are not suitable for studying the efficacy of therapy. Selection by prognostic factors (confounding by indication) may bias the results seriously. As Vandenbroucke reflected on this matter in 2004, "Observational studies should be restricted to questions that can meet the underlying assumption that the exposure allocation is unrelated to the outcome. Such restriction will be easiest for studies on adverse effects. Adverse effects are always unintended; their risk was not known at all,…"[24] Yet this may not always be true; if the risk of an adverse effect is known, it is possible that the treating clinicians will avoid the treatment in individuals at increased risk of the late complication concerned, especially if alternative treatment options are available. As long as the adverse effects of treatment are not

yet discovered, this potential bias does not yet play a role. This certainly holds for the patients in our study, who were all treated before 1987. First publications on late cardiac damage of radiation therapy for breast cancer emerged in the late 1980s.[25-28] In the present situation, however, with an accumulating amount of literature on the subject[4,5,29-33], and the growing awareness among attending specialists that these risks are probably not only a problem of the past, an observational study would already be somewhat more complicated.

One may wonder also whether the results of this hospital-based study are applicable to the general breast cancer population. Indeed, there may be differences in socioeconomic class and lifestyle factors. However, this does not influence the etiologic associations observed in our studies; there is no reason to believe that radiation-induced cardiac disease would not occur in a population-based study on late adverse effects, and the same holds for the occurrence of second cancers following adjuvant treatment. Nevertheless, the estimates of absolute excess risk may vary somewhat, because of a different distribution with regard to age and some lifestyle factors which may modify the treatment-related effects.

Finally, an inherent problem of retrospective studies evaluating late adverse effects is the replacement of the evaluated treatments by more modern treatments in the meanwhile. Results of the studies are therefore not always directly applicable to current clinical practice. Yet there are some other good reasons to perform this type of study.

- Logically, without these studies we would not have any notion of late effects, neither the presence nor the size of the problem;
- Identification of high risk groups may lead to a screening advice;
- Dose-response relationships established in these studies are useful in predicting future risk from current radiotherapy regimens for which follow-up data are not yet available.

Clinical implications

On the basis of our results, patients should not be withheld adjuvant treatments; rather should our study be considered as a late quality-control assessment. We must know the size and the impact of the various adverse outcomes before we can recommend changes in treatment regimens, techniques or indications.

When evaluating the impact of several types of late adverse effects, it is best to compare the absolute excess rates of the various events. If we would follow 1000 10-year survivors from our study for another 10 years, we would have expected 215 cardiac events to occur (based on incidence rates of the Dutch population) while we found 70 more events among the irradiated breast cancer patients, a 33% increase in risk (chapter 4). For lung cancer the expected absolute incidence rate was 3.8, while 9.6 cases of lung cancer were diagnosed per 10,000 irradiated patients per year (an excess of 5.8 per 10,000 patient-years, Table 7.3).

Table 7.3. Risk of second malignancies in irradiated patients of the Late Effects BC Study

	PYRS	O	E	SIR	AIR_{obs}	AIR_{exp}	AER
contralateral breast	49,428§	360	120	3.00	72.8	24.3	48.5
lung	60,577	58	23.3	2.48	9.6	3.8	5.8
esophagus	60,577	11	3.3	3.37	1.8	0.5	1.3

Abbreviations: PYRS, patient-years; O, observed number of events; E, expected number of events; SIR, standardized incidence ratio; AIR_{obs}, observed absolute incidence rate per 10,000 patient-years; AIR_{exp}, expected absolute incidence rate per 10,000 patient-years; AER, absolute excess risk per 10,000 patient-years.

$AIR_{obs} = O/PYRS * 10,000$

$AIR_{exp} = E/PYRS * 10,000$

$AER = (O – E)/PYRS * 10,000$

§ for risk of CBC, patients were censored at the time of distant metastasis.

Likewise, for esophageal cancer we expected 0.5, and observed 1.8 events per 10,000 patient-years (Table 7.3). Contralateral breast cancer was a different case; 24 events per 10,000 patient-years were expected, while 73 events per 10,000 patient-years were observed, an excess rate of 49 cases/10,000 patient-years (Table 7.3). However, also among non-irradiated patients the AER was substantial and amounted to 36 events per 10,000 patient-years, reflecting a hormone-related etiology or genetic predisposition for breast cancer[2], while 13 more events per 10,000 patient-years could be attributed to radiotherapy. Clearly, radiotherapy had more impact on cardiovascular disease than on contralateral breast cancer.

For the clinical implications we should make a distinction between patients treated in the past and future patients. As for all breast cancer survivors who have been treated with older radiotherapy methods, with potential harmful effects on the heart, we should give advice, preferably through their GPs, to treat or control any existing cardiovascular risk factors, like high blood pressure, diabetes mellitus, hypercholesterolemia, and of course, to stop smoking.

With regard to the implications for the patients treated tomorrow we cannot simply translate the results of our study to the treatment regimens of today's practice (see also section of "limitations of presented studies on late adverse effects"). Over the past years new techniques have been developed to treat breast, thoracic wall and regional lymph nodes more precisely and to spare normal tissues more effectively. With "Intensity Modulated Radiotherapy" (IMRT) the target volume is optimally irradiated using a large number of external beams, while the surrounding tissues will be spared.[34-37] "Image Guided Radiotherapy" enables more accurate patient set up and therefore the use of smaller safety margins. Whether treatment with modern techniques will prevent all late cardiac toxicity, must be evaluated in another 15 - 20 years.

As long as we are not sure about a threshold for radiation-induced cardiotoxicity, we recommend heart sparing techniques in the radiotherapeutic treatment of breast cancer.

Risk of CBC appears to be high in patients irradiated before age 40 specifically with photons on internal mammary chain and breast, and with a positive family history of breast cancer. With

IMRT the dose to the contralateral breast may be reduced to half of the dose received from conventional techniques[38-39]; yet, we should be very cautious when advising young breast cancer patients about a breast saving procedure, certainly when more relatives are affected. Moreover, in particular young patients from breast cancer families should be informed about the increased risk of developing a CBC after breast conserving techniques.

Recommendations for further research

Prospective studies examining the effects of radiation dose to specific structures of the heart on the risks of various cardiovascular diseases, preferably through intermediate endpoints, will be needed to find out which part of the heart is most radiosensitive and should be chosen as a reference point for tolerance doses. Also, these studies will enable us to establish a threshold dose for increased risk, if applicable.

As already mentioned, our finding of increased risk of heart failure after CMF in combination with radiotherapy should be evaluated in other large retrospective studies. For example, data from the Early Breast Cancer Trialists' Collaborative Group could be used to sort this out, on the condition that the follow-up is long enough. The SEER-registries in the USA, unfortunately, have no information on chemotherapy administration.

Furthermore, studies with prospective, extended monitoring will be essential to quantify the magnitude of the long-term toxicity profile of current cancer therapeutics, particularly with the increasing use of effective but cardiotoxic agents, like anthracyclines and trastuzumab. It is surprising that the late adverse effects of anthracyclines (doxorubicin and epirubicin) have been hardly studied so far.

Further research is warranted to evaluate our finding of increased risk of CBC among patients from breast cancer families who were irradiated at a young age. We had no information on mutation carrier status in these families and it is clinically relevant to find out whether germ-line mutations in BRCA1, BRCA2 or CHEK2 are involved, known as DNA-damage repair pathway genes, or other, still undiscovered gene mutations from so called non-BRCA1/2 breast cancer families. A recent case-only study reported that carriers of germline mutations in genes involved in the DNA-damage repair pathway have an increased risk (over and above the risk associated with their carrier status) of developing contralateral breast cancer after radiotherapy in comparison with non-carriers.[40]

Finally, we would like to emphasize that the availability of original medical records is essential for studies of long-term adverse treatment effects. Hopefully, the WGBO privacy law will be adapted along the lines proposed by the committee of the Health Council in 2004. Further destruction of medical data must be prevented. Since our studies showed that several late effects of treatment did not clearly emerge until 15 years after treatment, and the risk of

radiation-associated secondary malignancies appears to remain increased for at least 35 years, a retention period of at least 50 years rather than 30 years is recommendable.

Furthermore, future follow-up on adverse effects will be greatly facilitated by automated record linkage with population registries (Gemeentelijke Basis Administratie, GBA), the Netherlands Cancer Registry, and Statistics Netherlands (CBS).

With the introduction of the "Electronische Patiënten Dossier", EPD, a powerful tool has become available to obtain medical information both for patient care and research purposes. Obviously access to EPD must be arranged under strict regulations in order to guarantee the patient's privacy while improving the medical communication system.

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Summary

Breast cancer is by far the most frequent cancer among women in the Netherlands, with nearly 12,000 new female breast cancers diagnosed in 2006. Incidence rates have doubled since they became available in 1955, while breast cancer mortality remained almost unchanged. In view of this increased relative survival it has become exceedingly important to evaluate possible late adverse effects of treatment. Knowledge of long-term treatment effects may lead to modification of treatment regimens, techniques or indications in order to decrease the risk of adverse effects in future patients, while maintaining equal levels of therapeutic effectiveness. Of all late complications of treatment, cardiovascular disease and second malignancies are considered to be the most serious since they do not only cause substantial morbidity but also considerable mortality.

General aim of this thesis was to evaluate the long-term risks, both in terms of incidence and mortality, of second cancers, heart disease and cerebrovascular disease in survivors of breast cancer. Therefore, we conducted the Late Effects BC Study, a retrospective cohort study consisting of 7425 1-year survivors of breast cancer treated from the 1970s through the 1980s in two major cancer centers in the Netherlands.

Chapter 2 presents long-term cause-specific mortality among all 1-year survivors of the Late Effects BC Study. After a median follow-up of 13.8 years 4160 deaths were observed, of which 76% were due to breast cancer.

During follow-up, the relative risk of death from breast cancer declined, but even after more than 25 years since first treatment, patients still experienced a 6-fold increase of breast cancer mortality. Contrary to our expectations, overall cardiovascular mortality was not increased in our study population compared to the general population (standardized mortality ratio = 1.0). However, when we compared irradiated with non-irradiated patients within the cohort, adjusting for age and treatment period, radiotherapy was associated with a significant 1.7-fold increased risk of cardiovascular death. In absolute terms, irradiated patients experienced 19 excess deaths from cardiovascular disease per 10,000 patient-years. Postmastectomy radiotherapy showed a 2-fold increased cardiovascular mortality when applied before 1979, consistent with the literature on older radiation techniques, and then a decline in risk to a hazard ratio of 1.5 (95% CI: 0.9 - 2.7) when applied from 1979 on. For breast-conserving therapy irradiation administered in the latter period, we did not find an association with

increased risk of cardiovascular death (hazard ratio for breast conserving therapy vs. surgery only = 1.0; 95% CI: 0.5 - 1.9).
Second malignancies (excluding contralateral breast cancer) showed a slightly though significantly increased standardized mortality ratio of 1.16, corresponding with 5 excess deaths per 10,000 patient-years. Contralateral breast cancer contributed to only a small proportion (6%) of all breast cancer deaths, with 12 excess deaths per 10,000 patient-years.
In conclusion, patients irradiated after 1979 experience low (postmastectomy radiotherapy) or no (postlumpectomy radiotherapy) excess mortality from cardiovascular disease.

In **chapter 3** we report on the long-term risk of contralateral breast cancer in the 1-year survivors of the Late Effects BC Cohort, focusing on the effects of different radiation regimens, chemotherapy and family history of breast cancer.
Radiotherapy did not significantly increase the risk of contralateral breast cancer overall. However, the association with radiotherapy became stronger with younger age at breast cancer diagnosis (for age<35: hazard ratio = 1.78; 95% CI: 0.85 - 3.72; for age>45: hazard ratio = 1.09; 95% CI: 0.82 - 1.45). Furthermore, women treated before age 45 with postlumpectomy radiotherapy experienced 1.5-fold (95% CI: 1.11 - 2.09) increased risk of contralateral breast cancer compared with those who had postmastectomy radiotherapy. The dose-response relationship between radiation and risk of contralateral breast cancer became stronger when relating the radiation dose received by the medial portion of the breast to the development of contralateral breast cancer in the same area, supporting a role for radiation to induce malignancy in the contralateral breast. Our study is the first one examining the effects of combined exposure to radiotherapy and family history of breast cancer. For the subset of patients younger than 45, the joint effects of postlumpectomy radiotherapy and positive family history for breast cancer on risk of contralateral breast cancer were greater than expected when individual risks were summed (hazard ratio = 3.31; 95% CI: 1.96 - 5.60; *P* for departure from additivity = 0.045). Furthermore, we observed an association between adjuvant chemotherapy and decreased risk of contralateral breast cancer, but only in the first 5 years of follow-up; our data suggest that chemotherapy primarily affects contralateral breast cancer risk by eradicating pre-existing tumor cells in the contralateral breast.
Apparently young patients with a strong family history of breast cancer are more susceptible to radiation-induced breast cancer than patients without affected relatives. This finding should be taken into account when advising breast-conserving therapy in young breast cancer patients, particularly in mutation carriers, and warrants further research.

Next we studied treatment-specific incidence of cardiovascular disease in the 4414 10-year survivors of the Late Effects BC Study (**chapter 4**). After a median follow-up of almost 18 years, 942 cardiovascular events were observed (standardized incidence ratio = 1.30; 95% CI: 1.22 - 1.38; corresponding to 62.9 excess cases per 10,000 patient-years). Breast irradiation

only was not associated with increased risk of cardiovascular disease. However, radiotherapy to either the left or right side of the internal mammary chain was associated with increased cardiovascular disease risk for the treatment period 1970–1979 (for myocardial infarction, hazard ratio = 2.55; 95% CI: 1.55 - 4.19; *P*<.001; for congestive heart failure, hazard ratio =1.72; 95% CI: 1.22 - 2.41; *P*=.002) compared with no radiotherapy. Among patients who received internal mammary chain-radiotherapy after 1979, risk of myocardial infarction declined over time toward unity, whereas the risks of congestive heart failure (hazard ratio = 2.66; 95% CI: 1.27 - 5.61; *P*=.01) and valvular dysfunction (hazard ratio = 3.17; 95% CI: 1.90 - 5.29; *P*<.001) remained increased. Patients who underwent radiotherapy plus adjuvant chemotherapy (cyclophosphamide, methotrexate, and fluorouracil [CMF]) after 1979 had a higher risk of congestive heart failure than patients who were treated with radiotherapy only (hazard ratio = 1.85; 95% CI: 1.25 - 2.73; *P* = .002). Smoking and radiotherapy together were associated with a more than additive effect on risk of myocardial infarction (hazard ratio = 3.04; 95% CI: 2.03 - 4.55; *P* for departure from additivity = .039). In conclusion, radiotherapy as administered from the 1980s onwards is associated with an increased risk of cardiovascular disease. Irradiated breast cancer patients should be advised to refrain from smoking to reduce their risk for cardiovascular disease. Our finding of increased risk of congestive heart failure after adjuvant non-anthracycline containing chemotherapy warrants further research.

In **chapter 5** we describe treatment-specific risk of cerebrovascular events (stroke and transient ischemic attack) in all 10-year survivors of the Late Effects BC Study (*n* = 4414), accounting for cerebrovascular risk factors. Overall the risk of stroke was decreased by 25% in comparison with the general female population. Patients irradiated at the supraclavicular area and/or internal mammary chain did not experience a higher risk of stroke (hazard ratio = 1.0; 95% CI: 0.7 - 1.6) or TIA (hazard ratio = 1.4; 95% CI: 0.9 - 2.5) in comparison with patients who did not receive radiotherapy or were irradiated on fields other than supraclavicular area or internal mammary chain. Significantly increased risks of stroke were found in women who had received hormonal treatment (tamoxifen), and in women who had hypertension or hypercholesterolemia, with hazard ratios of 1.9, 2.1, and 1.6, respectively. From these data we may conclude that long-term survivors of breast cancer experience no increased risk of cerebrovascular events compared with the general population. Hormonal treatment is associated with an increased risk of stroke, while radiation fields including the carotid artery do not increase the risk of stroke compared with other fields.

In **chapter 6** we address the risk of cardiovascular disease following postlumpectomy irradiation restricted to tangential fields. We assessed the incidence of cardiovascular disease in 1601 patients with T1-2N0 breast cancer treated with breast tangentials in five different hospitals between 1980 and 1993. Patients treated with radiation fields other than breast tangentials and those treated with adjuvant chemotherapy were excluded. For patients with

left-sided breast cancer maximum heart distance was measured on the simulator films as a proxy for irradiated heart volume. Median follow-up was 16 years. The incidence of cardiovascular disease was 11.6% in patients with right-sided breast cancer versus 16.0% in left-sided cases. The hazard ratio associated with left-sided versus right-sided breast cancer was 1.38 (95% CI: 1.05 - 1.81) for cardiovascular disease overall, 1.35 (95% CI: 0.93 - 1.98) for ischemic heart disease, and 1.53 (95% CI: 1.09 - 2.15) for other heart disease. The risk of cardiovascular disease did not significantly increase with increasing maximum heart distance. In conclusion, patients irradiated for left-sided breast cancer with tangential fields have a higher incidence of cardiovascular disease compared with right-sided cancer. However, the risk does not seem to increase with larger irradiated heart volumes.

Finally, the general discussion in **chapter 7** considers some important issues related to the design and results of the Late Effects BC Study that have not been evaluated in the separate studies. In particular, we explained the approach of active follow-up and the specific new findings of our studies obtained through this approach. Furthermore we described mechanisms underlying cardiotoxicity of radiotherapy and chemotherapy. Results from the various Late Effects BC studies that seemed inconsistent with each other were discussed, as well as some limitations of studies on late adverse effects. We evaluated the impact of several adverse outcomes by comparing the absolute excess risks of the various events. The absolute excess risks for cardiac events were 70 per 10,000 irradiated patients per year, for lung cancer and esophageal cancer 5.8 and 1.3, respectively, and for contralateral breast cancer 13 per 10,000 irradiated patients per year. Clearly, the impact of radiotherapy on the occurrence of cardiovascular disease was higher than on second malignancies. Chemotherapy (CMF) in addition to radiotherapy seemed to further increase the risk of congestive heart failure compared with treatment with radiotherapy alone. The impact of chemotherapy on solid tumor risk was negligible apart from a temporarily protective effect on risk of contralateral breast cancer. Next we discussed clinical implications. With respect to cardiovascular disease, we made a distinction between patients treated in the past and future patients. Our advice to women who have been treated with older radiotherapy methods, with potential harmful effects on the heart, would be to control and/or treat any existing cardiovascular risk factors: high blood pressure, diabetes mellitus, hypercholesterolemia, and to stop smoking. As for the patients of tomorrow, we expect that with the introduction of Intensity Modulated Radiotherapy and Image Guided Radiotherapy, normal tissues will be spared more effectively. Whether these improvements in techniques will prevent all late cardiac toxicity, cannot be evaluated before another 15 - 20 years. For the time being, we recommend heart sparing techniques in the radiotherapeutic treatment of breast cancer. With respect to contralateral breast cancer, clinicians should be aware that the median time to contralateral breast cancer is 7.7 years, stressing the importance of surveillance for at least 10 years after the primary breast cancer diagnosis. Furthermore, in particular young patients from breast cancer families should be

informed about the increased risk of developing a contralateral breast cancer after whole breast irradiation with tangential fields. Recommendations for future research were presented: prospective studies will be needed to define the most radiosensitive part of the heart, and to establish a threshold dose for increased risk of cardiovascular disease. Our finding of increased risk of heart failure after CMF in combination with radiotherapy needs reaffirmation in other studies; moreover, the long-term toxicity profile of current cancer therapeutics, like anthracyclines and trastuzumab, should be evaluated as well. Further study is needed to evaluate the susceptibility to radiation-induced breast cancer in BRCA1/2 mutation carriers; possibly also other gene mutations are involved from non-BRCA1/2 breast cancer families. Our final remarks concern the privacy law in medicine (WGBO) that was introduced in 1995, allowing destruction of medical records after a period of 10 years. Obviously this action obstructs the evaluation of late effects of medical treatments in The Netherlands. The WGBO should be adapted along the lines proposed by the committee of the Health Council. Until the necessary changes in the law have been made, further destruction of medical data must be prevented.

Samenvatting

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen in Nederland, met bijna 12,000[1] nieuwe diagnoses gesteld in 2006. De incidentie-cijfers voor borstkanker zijn verdubbeld sinds 1955, terwijl de sterfte aan borstkanker nagenoeg gelijk bleef. Deze verbetering in relatieve overleving brengt met zich mee dat evaluatie van eventuele late nadelige effecten van de behandeling steeds belangrijker wordt. Inzicht in late complicaties van de behandeling zou kunnen leiden tot zodanige aanpassing van behandelings- schema's, -technieken en indicatiestellingen dat het risico op nadelige effecten voor toekomstige patiënten wordt verminderd terwijl tegelijkertijd de therapeutische effectiviteit gewaarborgd blijft.
Hart- en vaatziekten en tweede tumoren worden over het algemeen als de meest serieuze late nadelige behandelingseffecten beschouwd aangezien deze aandoeningen niet alleen ernstige ziekte maar ook aanzienlijke sterfte tot gevolg kunnen hebben.
De belangrijkste doelstelling van dit proefschrift was de evaluatie van de lange termijn risico's op tweede tumoren en hart- en vaatziekten, inclusief cerebrovasculair vaatlijden, bij overlevenden van borstkanker. Hiertoe werd de Late Effects Breast Cancer (BC) Study uitgevoerd, een retrospectieve cohortstudie van 7,425 1-jaar overlevenden van borstkanker die in de periode 1970-1986 werden behandeld in twee grote kankercentra in Nederland.

Hoofdstuk 2 beschrijft de oorzaak-specifieke sterfte over een lange follow-up periode voor alle 1-jaar overlevenden van de Late Effects BC Study. Na een mediane follow-up van 13.8 jaar waren 4160 vrouwen overleden, van wie 76% ten gevolge van borstkanker. In de loop van de follow-up nam het relatieve risico op overlijden aan borstkanker wel af, maar zelfs meer dan 25 jaar na de behandeling was de sterfte aan borstkanker nog altijd 6 maal verhoogd ten opzichte van de borstkankersterfte in de algemene vrouwelijke populatie. In tegenstelling tot onze verwachting was de algehele sterfte aan hart- en vaatziekten niet verhoogd in de studiepopulatie ten opzichte van de algemene populatie (Gestandaardiseerde Mortaliteit Ratio [SMR] = 1.0). Bij vergelijking echter van de bestraalde met de niet-bestraalde patiënten in het cohort bleek radiotherapie (RT) geassocieerd met een significant 1.7 verhoogd risico op cardiovasculaire sterfte, gecorrigeerd voor leeftijd en behandelperiode. In absolute

1. De getallen zijn weergegeven in de Angelsaksische notatie met een komma voor scheiding van de duizendtallen en met een decimale punt.

aantallen betekende dit dat op 1000 bestraalde patiënten die waren gevolgd over 10 jaar, er 19 meer overleden aan hart- en vaatziekten vergeleken met niet-bestraalde patiënten. Postmastectomie RT gegeven voor 1979 had een 2-voudig verhoogde cardiovasculaire sterfte tot gevolg, in overeenstemming met de literatuur over oudere radiatietechnieken, en vertoonde vervolgens een daling in risico voor de behandelperiode vanaf 1979 (Hazard Ratio [HR] = 1.5; 95% CI: 0.9 – 2.7). Voor postlumpectomie RT vonden we geen associatie met een verhoogd risico op cardiovasculaire sterfte (HR voor postlumpectomie RT vs geen RT = 1.0; 95% CI: 0.5 – 1.9).
De sterfte aan tweede primaire tumoren (contralateraal mammacarcinoom niet meegerekend) vertoonde een lichte maar wel statistisch significante stijging met een SMR van 1.16, overeenkomend met 5 extra overledenen per 10,000 patiënt-jaren. Contralateraal mammacarcinoom had slechts een bescheiden bijdrage (6%) aan de totale borstkankersterfte met 12 extra overledenen per 10,000 patiënt-jaren.
De belangrijkste conclusie is dat de cardiovasculaire sterfte voor patiënten bestraald na 1979 licht verhoogd is in geval van postmastectomie RT, en niet verhoogd in geval van RT gegeven voor borstsparende behandeling.

In **hoofdstuk 3** wordt het lange termijn risico op contralateraal mammacarcinoom (CBC) besproken bij de 1-jaar overlevenden van de Late Effects BC Study, met speciale aandacht voor de effecten van verschillende bestralingsschema's, chemotherapie en familiaire belasting voor mammacarcinoom. Over het geheel genomen gaf radiotherapie geen significant verhoogd risico op contralateraal mammacarcinoom. De associatie met radiotherapie werd echter wel sterker naarmate de diagnose borstkanker op jongere leeftijd werd gesteld (voor < 35 jaar: HR = 1.78; 95% CI: 0.85 – 3.72; voor > 45 jaar: HR = 1.09; 95% CI: 0.82 – 1.45). Borstwandbestraling na mastectomie met een direct elektronenveld gaf een significant lagere radiatieblootstelling in de contralaterale borst dan gehele borst-bestraling na een lumpectomie met tangentiele velden. Vrouwen die voor haar 45e jaar postlumpectomie bestraling hadden ondergaan, ondervonden 1.5 maal zo hoog risico op contralateraal mammacarcinoom in vergelijking met vrouwen die waren bestraald na een mastectomie. De gemiddelde radiatiedosis op het mediale deel van de contralaterale borst was hoger (3.8 Gy) dan op het laterale deel (1.3 Gy). We vonden dan ook een sterkere dosis-respons relatie tussen radiatie en het risico op contralateraal mammacarcinoom wanneer de radiatiedosis op het mediale deel van de contralaterale borst werd gerelateerd aan het voorkomen van mediaal gelegen contralateraal mammacarcinoom. Deze bevinding maakt een bijdrage van radiatie-geinduceerde carcinogenese in de contralaterale mamma aannemelijk. In onze studie is voor het eerst gekeken naar het gezamenlijke effect van radiotherapie en familiaire belasting voor borstkanker op het risico op contralateraal mammacarcinoom. Voor patiënten jonger dan 45 jaar bij diagnose bleek het gezamenlijke effect van postlumpectomie bestraling en een positieve familiegeschiedenis voor borstkanker groter dan verwacht op grond

van optelling van de afzonderlijke risico's (HR = 3.31; 95% CI: 1.96 – 5.60; *P* voor afwijking van additief model = 0.045).
Voor adjuvante chemotherapie vonden we een associatie met een verlaagd risico op contralateraal mammacarcinoom, maar alleen voor de eerste 5 jaren na behandeling. Deze bevinding wijst erop dat het effect van chemotherapie voornamelijk bestaat uit het uitschakelen van reeds aanwezige tumorcellen in de contralaterale mamma.
Samenvattend blijken jonge patiënten met een sterk familaire belasting voor borstkanker gevoeliger te zijn voor stralings-geinduceerd mammacarcinoom dan patiënten zonder familieleden met borstkanker. Deze bevinding dient meegenomen te worden bij de overwegingen ten aanzien van een borstsparende ingreep bij jonge borstkankerpatiënten, zeker bij BRCA1/2 genmutatiedraagsters, en zal verder moeten worden uitgezocht.

Vervolgens wordt de behandelings-specifieke incidentie van hart- en vaatziekten beschreven in de 4414 10-jaar overlevenden van de Late Effects BC Study (**hoofdstuk 4**). Na een mediane follow-up van bijna 18 jaar, vonden we 942 gevallen van hart- en vaatziekten, in absolute zin overeenkomend met 62.9 extra diagnoses per 10,000 patiënt-jaren (Gestandaardiseerde Incidentie Ratio = 1.30; 95% CI: 1.22 – 1.38). Bestraling van de borst alleen was niet geassocieerd met een verhoogd risico op hart- en vaatziekten. Bestraling van het parasternale veld, hetzij links hetzij rechts gegeven, gaf echter voor de periode 1970-1979 een toegenomen risico op hart- en vaatziekten in vergelijking met geen bestraling (HR voor myocard infarct = 2.55; 95% CI: 1.55 – 4.19; *P*<.001; HR voor hartfalen = 1.72; 95% CI: 1.22 – 2.41; *P* = .002). Bij patiënten bestraald op het parasternaal veld na 1979 was het risico op een myocard infarct niet meer verhoogd, in tegenstelling tot de risico's op hartfalen (HR = 2.66; 95% CI: 1.27 – 5.61; *P* = .01) en klepafwijkingen (HR = 3.17, 95% CI: 1.90 – 5.29; P<.001). Patiënten die na 1979 waren behandeld met radiotherapie en adjuvante chemotherapie (cyclophosphamide, methotrexaat en fluorouracil [CMF]) hadden een hoger risico op hartfalen dan patiënten die alleen met radiotherapie waren behandeld (HR = 1.85; 95% CI: 1.25 – 2.73; *P* = .002). Het gecombineerde effect van roken en bestraling op het risico van een hartinfarct was groter dan verwacht op grond van optelling van de afzonderlijke risico's (HR = 3.04; 95% CI: 2.03 – 4.55; *P* voor afwijking van additief model = .039).
De belangrijkste conclusie is dat ook radiotherapie uit de jaren '80 is geassocieerd met een verhoogd risico op hart- en vaatziekten. Bestraalde borstkankerpatiënten moet worden geadviseerd om te stoppen met roken teneinde hun risico op hart- en vaatziekten terug te dringen. Het effect van niet-anthracycline bevattende chemotherapie op het toegenomen risico op hartfalen dient verder te worden uitgezocht.

In **hoofdstuk 5** beschrijven we het behandelings-specifieke risico op cerebrovasculaire aandoeningen (CVA en TIA) in de 4414 10-jaar overlevenden van de Late Effects BC Study. Over het geheel genomen was het risico op CVA in de studiepopulatie 25% lager dan in de al-

gemene vrouwelijke bevolking. Voor patiënten bestraald op het supraclaviculaire gebied en/of het parasternale veld was het risico op CVA niet verhoogd (HR = 1.0; 95% CI: 0.7 – 1.6) ten opzichte van patiënten die niet met radiotherapie waren behandeld of die waren bestraald op velden gelegen buiten het supraclaviculaire of parasternale gebied. Toegenomen risico's op CVA werden gevonden bij vrouwen die hormonale therapie (tamoxifen) hadden gehad, en bij vrouwen bekend met hypertensie of hypercholesterolemie, met HRs van respectievelijk 1.9, 2.1 en 1.6.
Uit deze resultaten volgt dat lange termijn overlevenden van borstkanker geen verhoogd risico op cerebrovasculaire aandoeningen hebben in vergelijking tot de algemene bevolking. Hormonale behandeling is geassocieerd met een toegenomen risico op CVA, terwijl bestralingsvelden waarin de arteria carotis is gelegen geen verhoogd risico op CVA geven ten opzichte van andere velden.

Hoofdstuk 6 behandelt het risico op hart- en vaatziekten na borstbestraling met alleen tangentiele velden. Voor deze studie combineerden we de gegevens van de patiënten behandeld met tangentiele velden uit de Late Effects BC study met gegevens van patiënten uit vier andere ziekenhuizen die dezelfde behandeling hadden ondergaan. Bij in totaal 1601 patiënten, allen behandeld voor borstkanker stadium T1-2,N0 in de periode 1980-1993, werd de incidentie van cardiovasculaire ziekten bepaald. Patiënten bestraald op andere velden of behandeld met adjuvante chemotherapie, waren uitgesloten van de studie. Van alle patiënten met linkszijdige borstkanker werd op simulator films de zogenaamde "maximum heart distance" gemeten, de maximale afstand tussen de achterste veldgrens van het tangentiele borstveld en de hartcontour, als een benadering voor het bestraalde hartvolume. Na een mediane follow-up van 16 jaar was de incidentie van cardiovasculaire ziekten 11.6% bij patiënten met rechtszijdige borstkanker, en 16% bij patiënten met linkszijdige borstkanker. Linkszijdige versus rechtszijdige borstkanker was geassocieerd met een verhoogd risico op cardiovasculaire aandoeningen (HR = 1.38; 95% CI: 1.05 – 1.81); HRs voor ischemische hartziekten (ICD-9, 410-414) en andere hartaandoeningen (ICD-9, 420-429) waren respectievelijk 1.35 (95% CI: 0.93 – 1.98) en 1.53 (95% CI: 1.09 – 2.15). Er was geen significante toename van het risico op cardiovasculaire aandoeningen met het toenemen van de gemeten maximale hartafstand.
Concluderend hebben patiënten bestraald met tangentiele velden voor linkszijdige borstkanker een hoger risico op cardiovasculaire ziekten dan patiënten met rechtszijdige borstkanker. Het risico neemt echter niet toe met het groter worden van het bestraalde hartvolume.

Ten slotte wordt in de algemene discussie van **hoofdstuk 7** een aantal belangrijke onderwerpen besproken die te maken hebben met de opzet en de resultaten van de Late Effects BC Study, en die nog niet eerder in de afzonderlijke artikelen aan de orde waren geweest. De toepassing van een actief follow-up beleid wordt uitgelegd, gevolgd door een opsomming van nieuwe bevindingen uit onze studies die zijn verkregen met behulp van deze aanpak.

Vervolgens worden mechanismen geschetst die ten grondslag (kunnen) liggen aan de cardiotoxiciteit van radiotherapie en chemotherapie. Sommige resultaten uit de voorgaande artikelen die met elkaar in tegenspraak lijken, worden verder toegelicht en ook komen beperkingen van late-effecten studies aan bod. We beoordelen de impact van verschillende nadelige effecten door de absolute extra risico's van de betreffende aandoeningen te vergelijken. Het absolute extra risico op cardiale aandoeningen was 70/10,000 bestraalde patiënten per jaar; voor longkanker, slokdarmkanker en contralateraal borstkanker bedroeg dit extra risico respectievelijk 5.8, 1.3, en 13 per 10,000 bestraalde patiënten per jaar. De invloed van radiotherapie op het vóórkomen van cardiovasculaire aandoeningen was duidelijk hoger dan op het optreden van secundaire maligniteiten. Behandeling met chemotherapie (CMF) en radiotherapie gaf een sterkere toename van het risico op hartfalen dan behandeling met radiotherapie alleen. Voor chemotherapie vonden we geen effect op de ontwikkeling van solide tumoren afgezien van een tijdelijk beschermend effect op het voorkomen van contralateraal mammacarcinoom. De klinische implicaties worden besproken. Voor wat betreft cardiovasculaire ziekte dient er onderscheid gemaakt te worden tussen patiënten die in het verleden zijn behandeld en toekomstige patiënten. Vrouwen die met oudere radiatietechnieken zijn behandeld, met potentieel schadelijke effecten op het hart, zouden we willen adviseren om risicofactoren voor hart- en vaatziekten te laten controleren en behandelen, zoals hypertensie, suikerziekte en hypercholesterolemie, en te stoppen met roken. Voor toekomstige patiënten is de verwachting dat met de komst van "Intensity Modulated Radiotherapy" en "Image Guided Radiotherapy" de omliggende gezonde weefsels beter kunnen worden gespaard. Of deze technieken geen late hartschade tot gevolg hebben, zal toekomstig onderzoek moeten uitwijzen. Tot het zover is, lijkt het raadzaam om hartsparende technieken toe te passen bij de radiotherapeutische behandeling van borstkanker. Het gegeven dat de mediane tijd tot het optreden van een contralateraal mammacarcinoom in onze studie 7,7 jaar was, onderstreept het belang van controle gedurende ten minste 10 jaar na de diagnose van het eerste mammacarcinoom. Ook dienen jonge patiënten uit erfelijk belaste borstkankerfamilies te worden voorgelicht over het extra risico op het ontwikkelen van contralateraal mammacarcinoom na borstbestraling met tangentiele velden. Ideeën voor verder onderzoek worden genoemd. Nog steeds is niet duidelijk wat de meest stralengevoelige structuur van het hart is; hiervoor zijn prospectieve studies nodig. Tevens dient te worden uitgezocht of er ten aaanzien van de radiatiedosis een drempelwaarde bestaat waarboven het risico op cardiovasculaire ziekte begint toe te nemen. We vonden een verhoogd risico op hartfalen na CMF in combinatie met radiotherapie; dit effect zal bevestigd moeten worden in andere studies. Nog veel belangrijker is het dat er aandacht komt voor de cardiotoxische effecten op langere termijn van meer recent gebruikte kankergeneesmiddelen, zoals anthracyclines en trastuzumab. Verder onderzoek is nodig om de gevoeligheid voor radiatie-geinduceerde borstkanker bij BRCA1/2 mutatiedraagsters te bestuderen; wellicht spelen nog andere, tot nu toe onbekende genmutaties een rol.

Tot slot worden er zorgen geuit over het vernietigende effect van de invoering van de Wet Geneeskundige Behandelings Overeenkomst in 1995, waarin werd vastgelegd dat medische dossiers slechts 10 jaar bewaard mochten worden. Het mag duidelijk zijn dat onderzoek naar late effecten van medische behandelingen hiermee in Nederland volstrekt onmogelijk wordt. Na een rapport van de Gezondheidsraad uit 2004 werd de vernietigingsverplichting - die 1 april 2005 zou ingaan - vlak voor die datum voorlopig ongedaan gemaakt door de bewaartijd te verlengen van 10 naar 15 jaar. Op 1 april 2010 loopt de overgangsperiode af, en er is dringend behoefte aan een wetswijziging waarin wordt voorzien in een veel ruimere bewaartijd van ten minste 50 jaar. Ondertussen gaat de vernietiging van medische dossiers onverminderd door. Vinden we dat erg? Vast wel…

Dankwoord

Voor het welslagen van een promotietraject is meer nodig dan doorzettingsvermogen en een academische titel. Zeker zo belangrijk zijn de mensen erom heen: mensen die helpen bij het vormgeven van de inhoud, en mensen die helpen bij het organiseren van het dagelijks leven. Ik wil iedereen bedanken die direct of indirect heeft bijgedragen aan de totstandkoming van dit proefschrift. Een paar mensen wil ik in het bijzonder noemen.

Joop van Dongen. Beste Joop, dit verhaal begint bij jou; onder jouw inspirerende begeleiding is mijn belangstelling voor borstkankeronderzoek ontstaan tijdens een wetenschappelijke stage in het NKI. In latere jaren heb jij het contact gelegd tussen Floor en mij, wat nu dan heeft geresulteerd in dit proefschrift. Ik waardeer het bijzonder dat je in mijn commissie hebt willen plaats nemen.

Floor van Leeuwen. Beste Floor, jouw gedrevenheid gepaard aan een scherpe analytische geest en een feilloos gevoel voor presentatie zowel op schrift als voor publiek maken je tot een inspirerend voorbeeld. Met het enthousiasme dat jij uitstraalt lijkt de helft van het project al geklaard. Wat in de realiteit natuurlijk wel eens blijkt tegen te vallen… Maar ik heb wel geleerd hoe belangrijk bezielende leiding voor het welslagen van een project is. Ik kwam van heel ver, letterlijk en figuurlijk, uit een expat-bestaan in Nigeria met weliswaar de nodige medische kennis maar met slechts een klein beetje ervaring in de epidemiologie. Je gaf me alle vertrouwen, en hoewel het project vrij strict omschreven was en bovendien reeds liep toen ik begon, heb ik alle ruimte gekregen om er mijn eigen draai aan te geven en er de onderwerpen uit te lichten die mij aanspraken. Voor dit alles wil ik je heel hartelijk danken, en ik ben heel blij dat ik een aantal jaren onder jouw supervisie heb mogen leren en werken.

Berthe Aleman. Beste Berthe, jij was een lichtend baken in roerige tijden. Altijd rustig en beschouwend, wist je de zaken weer te relativeren, en, heel belangrijk, te vertalen naar de relevantie voor de kliniek. Het waren voor jou zelf bij tijd en wijle zware tijden: de kliniek, je eigen promotieonderzoek, je werkzaamheden bij de lymfoom groep, en dan ook nog de begeleiding van o.a. dit project. Je hebt heel wat zondagen besteed aan de revisie van mijn artikelen, die altijd weer per omgaande post in mijn In-box belandden. Dan waren er de terugkerende onderwerpen van discussie, o.a. jouw overtuiging dat de winst ten gevolge van RT meer over het voetlicht moest komen. Keer op keer hebben we gezocht naar een

formulering waarin de goede en nadelige gevolgen van RT voor alle partijen voldoende in balans waren. Dank je wel voor alle hulp en advies!
Marianne Kuenen. Beste Marianne, jij verdient een bijzonder dankwoord. Ik heb vaak gedacht: zonder jou was dit project niet zover gekomen, en was met name de follow-up niet zo compleet geweest. (Maar: met een kopje koffie erbij moet het lukken…!) Jouw toewijding en de vriendelijke vasthoudendheid waarmee jij huisartsen wist te achtervolgen en te overtuigen om toch de vragenlijst in te vullen waren hartverwarmend. En tja, zonder humor waren we er natuurlijk ook niet gekomen. Jouw lach daverde regelmatig over de afdeling en werkte zeer aanstekelijk op andere aanwezigen. Heel erg bedankt voor je enorme inzet die veel verder voerde dan er in welk contract dan ook kan worden vastgelegd.
Gabey Ouwens. Beste Gabey, vol bewondering en nog meer opluchting heb ik toegekeken hoe jij met grote voortvarendheid de laatste losse einden van de MHD-studie hebt opgepakt en tot een goed einde gebracht. Klasse!
Natuurlijk zijn er nog meer onderzoeksmedewerkers belangrijk geweest voor het welslagen van dit project; graag wil ik Maureen Beelen, Vivianne Hartog, Jojanneke van der Swaluw, Steffi Kraus, Shula Grivell, Gijs Besseling, en Anne-Wil van der Meij bedanken voor hun bijdrage.
Sandra van den Belt-Dusebout en Mathilde Cardous-Ubbink. Beste Sandra en Mathilde, onze opdrachten lagen niet ver uit elkaar, en daarmee liepen we ook tegen dezelfde problemen aan. En gedeelde problemen zijn nu eenmaal minder groot… Sandra, zeker in de beginperiode heb ik dankbaar gebruik gemaakt van jouw enorme ervaring op het gebied van tweede tumoren onderzoek. Inmiddels is jouw project ook bijna volbracht; succes met de laatste loodjes! Mathilde, ook voor jou is het einde in zicht.
Agnes van Rosmalen en Akke Botma. Beste Agnes en Akke, beide hebben jullie je afstudeerwerk verricht op mijn project. Ik vond het geweldig leuk om jullie te begeleiden, en heb er veel van geleerd. Dank voor jullie inzet en enthousiasme, en jullie bijdrage aan dit onderzoek.
Lucille Dorresteijn. Beste Lucille, met veel plezier denk ik terug aan onze samenwerking; het overleg was altijd gezellig maar ook constructief. Hartelijk dank voor je enthousiaste inzet en je bereidheid om altijd weer meer te doen. Ik hoop van harte dat ons artikel ook nog kan bijdragen aan de voltooiing van jouw proefschrift!
Jacques Borger. Beste Jacques, jij had een interessant idee, en wij hadden (meer) data om het idee te toetsen. Dank voor je bereidheid om dit project samen uit te voeren; dit heeft een mooi artikel opgeleverd.
Willem Klokman. Beste Willem, met behulp van jouw persoonsjarenanalyse zijn al heel wat resultaten – en papers – gegenereerd. Ook ik heb er meermalen dankbaar gebruik van gemaakt.
Michael Hauptmann. Beste Michael, dank je wel voor jouw bijdrage in de statistiek; ik begrijp dat je zo nu en dan wanhopig wordt van eigengereide epidemiologen. Dank daarom ook voor je flexibele opstelling en je bereidheid om je adviezen aan te passen aan een epidemi-

ologische benadering zonder daarbij concessies te doen aan de essentiele voorwaarden van een nette analyse.
Matti Rookus. Beste Matti, hoewel je niet direct bij mijn project betrokken was, had ik wel het gevoel dat ik altijd voor advies bij je binnen kon stappen – en dat was ook zo. Je hebt me een aantal malen met raad en daad bijgestaan. Dank!
Graag wil ik hierbij ook alle andere NKI-collega's – van binnen en buiten de PSOE - bedanken die meeleefden met alle presentatie-, publicatie-, en promotieperikelen.
Jan Klijn en Caroline Seynaeve. Beste Caroline en Jan, het heeft allemaal toch wat langer geduurd… jullie wil ik heel hartelijk danken voor het geduld dat jullie met mij hebben getoond in de afronding van dit proefschrift.
Agnes van der Gaag. Beste Agnes, dank je wel voor de prachtige omslag die je speciaal voor mijn boekje hebt gemaakt. Het was voor mij heel zinvol om eerst onder woorden te brengen wat ik precies op de voorkant tot uitdrukking wilde brengen. Je hebt het heel goed aangevoeld, dank hiervoor!
Mijn gezin. Lieve Jo en Fiek, jullie weten hoe het is om er "helemaal voor te gaan". Dank voor jullie medeleven en begrip; ik weet dat ik er niet altijd was als jullie me nodig hadden, maar jullie zijn er wel heel zelfstandig van geworden!
Lieve Bram, laatst zei jij al: "als mama is gepromoveerd, krijgen we allemaal een cadeautje, want dan heeft ze weer meer tijd voor ons." Die tijd breekt nu echt aan!
Lieve Jan Dirk, jij weet het beste hoezeer ik ook heb geworsteld met dit project; niet zozeer inhoudelijk maar vooral met de tijdsbalans die te vaak was doorgeslagen naar werk ten koste van privé en gezin. Ik ga niet zeggen dat het nooit meer druk wordt, dat doe jij ook niet, maar laten we toch iets meer streven naar de Noorse benadering van leven: werken om te leven in plaats van leven om te werken. Er is nog zoveel meer de moeite waard in dit bestaan!

Curriculum vitae

Maartje Hooning werd geboren op 6 augustus 1962 te Haarlem. In 1980 behaalde zij haar Gymnasium-β diploma aan het Gymnasium Celeanum te Zwolle en begon na een kort verblijf aan de LU te Wageningen met de studie geneeskunde aan de UVA te Amsterdam. Haar wetenschappelijke stage in het kader van haar studie verrichtte zij in het Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis onder supervisie van Prof. Dr. J.A. van Dongen. Na het behalen van het arts-diploma in 1990 werkte zij een jaar als algemeen arts-assistent in dienst van de maatschappen Interne Geneeskunde, Longziekten en Cardiologie in ziekenhuis De Heel te Zaandam. Na de geboorte van haar eerste kind zocht ze een baan als arts-onderzoeker op de afdeling interne oncologie van het Erasmus MC, Daniel den Hoed Cancer Center. Van 1993 tot 1999 verbleef zij met man en kinderen in het buitenland alwaar zij zich specialiseerde in allerhande niet-medische zaken. In 1999 begon zij met een MSc-opleiding clinical epidemiology aan het Netherlands Institute for Health Sciences in Rotterdam en in 2000 met het promotie-onderzoek "Adverse effects of treatment in long-term survivors of breast cancer" op de afdeling Psychosociaal Onderzoek en Epidemiologie van het Nederlands Kanker Instituut/Antoni van Leeuwenhoek Ziekenhuis, onder supervisie van Prof. Dr. Ir. F.E. van Leeuwen. De MSc-opleiding werd afgerond in 2001. Momenteel is zij als epidemioloog verbonden aan de Werkgroep Erfelijke Tumoren (onder voorzitterschap van Prof. Dr. J.G.M. Klijn) binnen de afdeling interne oncologie van het Erasmus MC, Daniel den Hoed Cancer Center te Rotterdam.